A CLINICAL METHOD OF ASSESSING THE RESULTS OF THERAPY IN THYROTOXICOSIS

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THYROTOXICOSIS may be treated surgically, by radioactive iodine, or by one of the antithyroid drugs. Whichever method is chosen the clinician must decide whether or not his treatment has been effective. His conclusions are based on the gradual disappearance of a number of abnormal symptoms and signs. Different observers may attribute differing degrees of significance to these changes and for this reason it is desirable that the same person should carry out the interview and examination at each visit. But even when this is practicable the observer may find it difficult to decide on the relative importance which should be attached to different clinical features especially if they are in conflict—for example, to a reduction in the degree of tachycardia combined with a failure to gain weight. That the inaccuracy inherent in a purely clinical assessment of the regression of the disease is real is shown by comparing the conclusion of Bartels (1945) that thiobarbitone is 12 times more active in thyrotoxicosis than thiouracil with that of Astwood (1945) who found it to be only twice as active.

The alternative method of following a patient's progress by repeated estimations of the basal metabolic rate (B.M.R.) is time-consuming and inconvenient for the patient. In addition it is necessary to allow for the effect of training, and because of the wide normal range the method is applicable only to groups of patients and the results must be treated statistically. Since diagnostic tests using radioactive iodine give misleading results in a patient receiving an antithyroid drug this parameter of thyroid function cannot be used in assessing therapeutic response.

We have approached this problem of assessing the response to treatment in a new way. In a previous investigation we were able to allocate figures indicating the relative diagnostic value of the various symptoms and signs of thyrotoxicosis. To do this we carried out an analysis of their comparative frequency in patients with the disease and in normal individuals. From these we derived a total score which we called the diagnostic index and which we have been able to show has about the same degree of diagnostic accuracy as estimations of the B.M.R., or the results of radioactive-iodine studies (Crooks et al. 1959). By removing from the list of these diagnostic features of thyrotoxicosis those which are unaffected by treatment we have now constructed a therapy index which gives a quantitative measure of the response to treatment. This paper describes our method. We illustrate its application by comparing two antithyroid drugs, methylthiouracil and potassium perchlorate.

Material and Methods

We first studied 40 thyrotoxic patients with diffusely enlarged thyroid glands and exophthalmos—that is to say, they formed a homogeneous group exhibiting classical Graves' disease.

All were admitted to hospital and the diagnosis was confirmed by radioactive-iodine studies, including the 4-hour uptake of ^{131}I and the 48-hour plasma-protein-bound radioactivity. B.M.R.s and serum-cholesterol values were also estimated.

The patients were allocated to two groups, one to be given methylthiouracil and the other potassium perchlorate. Methylthiouracil was given in the doses we use routinely—namely, 200 mg. three times a day for two weeks, followed by 100 mg. three times a day. Potassium perchlorate was given in a dose of 200 mg. three times a day which is the dose originally used by Godley and Stanbury (1954).

Before treatment began, the patients were discharged from hospital and instructed to attend weekly. At the first outpatient attendance they were examined by a standard routine. Each subject was weighed in her clothes and asked to wear the same clothing on subsequent visits. She was then instructed to lie down on an examination couch and was left undisturbed for 10 minutes. The resting pulse-rate was counted for 1 minute and the presence or absence of the symptoms and signs shown in table I was recorded. The history was taken and the physical examination was carried out in the same way for each patient, the criteria for the identification of symptoms and signs being those laid down by Crooks et al. (1959), except in the case of the pulse-rate where a resting rate higher than 85 beats per minute was scored as abnormal. Throughout the series all observations, with a few exceptions, were made by one of us (J. C.), whose observations in previous observer-variation studies involving the clinical features shown in table I did not differ significantly from those of 7 other experienced observers (Crooks et al. 1959).

Numerical values were allocated to each clinical feature (table I) on the basis of their diagnostic significance (Crooks et al. 1959) except in the case of appetite increase and weight loss. We had previously established that the combination of these two symptoms was of great diagnostic importance, and for the purpose of diagnosis each was rated +3 giving a value of +6 if both were present. In the assessment of therapeutic response, however, the restoration of weight loss is of much greater significance than the return of the appetite to normal, and for this reason the rating for the symptom of weight loss was increased to +4 and that for increase of appetite reduced to +1. By adding the values obtained after the first outpatient

TABLE I—WEIGHTING FACTORS ALLOCATED TO THE SYMPTOMS AND SIGNS OF THYROTOXICOSIS

Thyrotoxicosis-therapy index

Symptoms	Score +1	Signs	Score +4
Dyspnœa on effort	+1	Hyperkinetic movements	
Palpitations	+2	Fine finger tremor	+1
Tiredness	+2	*Hands:*	
Preference for cold	+5	Hot	+2
Excessive sweating	+3	Moist	+1
Nervousness	+2	*Resting pulse-rate:*	
Appetite increased	+1	More than 85 per min.	+3
Weight decreased *	+4		

* For each 4 lb. weight gain deduct 1 point.

TABLE II—CHANGES IN BASAL METABOLIC-RATES (ROBERTSON AND REID)

Patient no.	Potassium perchlorate: Initial (before therapy) %	Potassium perchlorate: Final* (after therapy) %	Patient no.	Methylthiouracil: Initial (before therapy) %	Methylthiouracil: Final* (after therapy) %
1	+75	+9	21	+22	−14
2	+27	−6	22	+74	−17
3	+20	+14	23	+45	−14
4	+47	+9	24	+27	+10
5	+21	+4	25	+51	+6
6	+28	+2	26	+84	−14
7	+32	−21	27	+71	−5
8	+8	−18	28	+36	−13
9	+67	+14	29	+54	−8
10	+76	−3	30	+23	−14
11	+40	+8	31	+42	+8
12	+60	+14	32	+71	−4
13	+46	+14	33	+17	−12
14	+26	−9	34	+41	+8
15	+33	−5	35	+45	+2
16	+17	−17	36	+47	+8
17	+42	+3	37	+46	−8
18	+20	0	38	+43	−2
19	+13	−12	39	+47	+1
20	+16	−1	40	+53	+4
Mean	+35·7	0·0 (SD 10·6)	Mean	+47·0	−3·9 (SD 9·2)

* Taken nearest to week in which the patient reached a therapy index of 5 or less.

attendance a total score, which we term the therapy index was derived for each patient.

At the first outpatient visit treatment began and alternate patients were given methylthiouracil or potassium perchlorate. The patients receiving potassium perchlorate were instructed not to eat fish or iodised salt and to avoid medicines containing iodine.

At each subsequent weekly visit the procedure for ascertaining body-weight, resting pulse-rate, and the presence or absence of the clinical features of the disease was repeated. When a symptom or sign disappeared completely its value was deducted from the therapy index of the previous week. In the case of weight increase one point was deducted from the initial index for each 4 lb. of weight gained. In this way a fresh index was calculated weekly for each patient. B.M.R. estimations were carried out in all patients at two-weekly intervals. The technique used was that described by Crooks et al. (1958).

Complete remission of the disease or " cure " was taken to have occurred when the therapy index reached and remained within the range 0–5 for three successive weeks. The actual week of " cure " was chosen as that week with the lowest of the 3 values. This range was adopted since indices greater than 5 are obtained if two clinical features conventionally regarded as of high diagnostic significance are present simultaneously (table I). Strong confirmation that the range 0–5 indicates full control of the disease was afforded by the estimations of the B.M.R. (table II). Further confirmation was obtained by the observation that in patients who were satisfactorily controlled by antithyroid drugs, indices fluctuated within this range for long periods.

When the patient was euthyroid she was given maintenance doses of the drugs ranging from 50 to 150 mg. daily for methylthiouracil, and 200 to 400 mg. daily for potassium perchlorate. After 3 months maintenance therapy administration of the drugs was stopped. 14 of the 40 cases (series 1) relapsed and then formed a separate group (series 2). In this investigation patients acted as their own controls. The design was similar to that of the " cross-over " method used by pharmacologists for the biological assay of substances such as insulin. Thus 8 subjects of series 1 who had been given methylthiouracil, and who had relapsed when therapy was stopped, were retreated with potassium perchlorate. Similarly 6 subjects who had been treated with potassium perchlorate were retreated with methylthiouracil. The same dosage schemes for each drug were used in retreatment as in the initial treatment and the follow-up procedure was identical. Progress was checked by repeated estimations of the B.M.R.

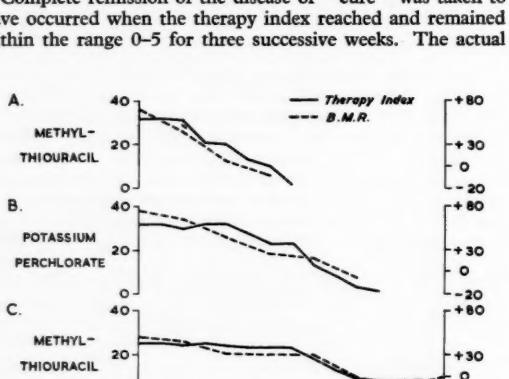

Fig. 1—Rate of change in the therapy index and the B.M.R. during treatment with methylthiouracil and potassium perchlorate (600 mg. daily). A and B show linear changes of the therapy indices with time. B and C show the delayed type of therapeutic response.

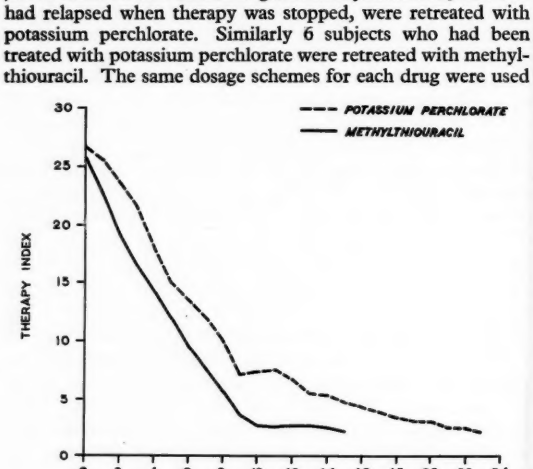

Fig. 2—Rate of change of the mean therapy index produced by potassium perchlorate and methylthiouracil in 2 groups of 20 patients (series 1).

Results

Series 1 (Time taken to " cure ")

The number of patients reaching the level we have defined as " cure " at any given time is shown in table III. The mean time to " cure " of the 20 patients receiving methylthiouracil was 9·1 weeks, and the comparable figure for the 20 patients receiving potassium perchlorate was 13·1 weeks. These values are significantly different ($P < 0.01$). It can be seen from table III that in the group of patients receiving potassium perchlorate the longest time taken to effect " cure " was 23 weeks compared with 15 weeks for methylthiouracil. It also shows the larger number of patients receiving perchlorate who required long courses before " cure " was achieved.

Variations of Therapy Index with Time

Typical examples of the changes in the index during therapy are shown in figs. 1A (methylthiouracil) and B (potassium perchlorate). The associated changes in the basal metabolic rate plotted on the same figures show good agreement with the clinical method of assessment.

TABLE III—DISTRIBUTION OF PATIENTS IN SERIES 1 RECEIVING METHYLTHIOURACIL AND POTASSIUM PERCHLORATE (600 mg. DAILY) SHOWING TIME TAKEN TO EFFECT " CURE "

Time to effect " cure " (weeks)	Methylthiouracil (no. of patients)	Potassium perchlorate (600 mg. daily) (no. of patients)
3–4	1	..
5–6	3	..
7–8	4	5
9–10	10	3
11–12	1	4
13–14	..	3
15–16	1	..
17–18	..	2
19–20	..	1
21–22	..	1
23–24	..	1
Total	20	20
Mean time to " cure "	9·1 weeks	13·1 weeks

In the case of both patients illustrated in these figures linear regressions of the therapy indices on time showed a significant fall in the values of the index with time. This relationship was found to hold in 17 of the 20 patients treated with methylthiouracil. The remaining 3 patients were slow to respond to the drug, and the changes both in the therapy index and in the basal metabolic rate in this type of response are shown in fig. 1C. The indices of all 3 patients, however, reached values of 5 or less in subsequent weeks. Of the 20 patients treated with potassium perchlorate, 16 showed falls in the value of the index with time which were significant. In 1 of the remaining 4 patients the values of the index suggested that the reason for the non-significant fall was the absence of data on three occasions on which she defaulted. The remaining 3 patients did not respond to treatment until 6 weeks or more had elapsed and an example of this type of response to perchlorate is shown in fig. 1D.

Fig. 2 shows the changes in the mean therapy index with time for each group of 20 patients. The more rapid improvement in patients treated with methylthiouracil as compared with potassium perchlorate is clearly seen. This method of comparing the effectiveness of the two drugs is, however, statistically unsatisfactory because of the two types of therapeutic response obtained with each drug. For example the mean curves for both drugs show a uniform decrease in the value of the index for the first few weeks of treatment and the variations of the type shown in fig. 1C and D are concealed. It was for this reason that we did not compare the effectiveness of the drugs by the rate of change of the therapy index but adopted the time taken to effect " cure " as the criterion of therapeutic response.

Effect of Initial Values of the Therapy Index

A comparison between the initial values of the therapy indices and the times taken to effect " cure " showed that for the groups on either drug there was no significant correlation between these two variables. In other words, the time taken to effect " cure " was uninfluenced by the initial degree of severity of the disease.

Basal Metabolic Rate

The mean values of B.M.R.s in the patients of both groups of series 1 before and after therapy are shown in table II. These do not exactly correspond to the times when the patients had reached the week of " cure ". The reason for this discrepancy is that the values of B.M.R.s were obtained at fortnightly intervals, whereas the therapy indices were obtained at weekly intervals. For the 20 patients treated with methylthiouracil the mean value after therapy of −3·9 corresponds to a time 0·55 week before the week of " cure "; for the 20 patients on potassium perchlorate the mean value after therapy of 0·0 corresponds to a time 0·35 week before the week of " cure ". 2 patients who received potassium perchlorate had B.M.R.s below the usually accepted upper limit of the normal range but were thyrotoxic by all other criteria, including radioactive-iodine tests. We have previously pointed out that this may occur and that in such cases the B.M.R. falls with treatment (Crooks et al. 1958).

At the beginning of treatment using methylthiouracil the mean value of the B.M.R.s for the 20 patients was +47·0; at the conclusion or rather at 0·55 week before " cure " the mean value was −3·9 with a standard deviation of 9·2. A normal group of individuals would be expected to have a B.M.R. whose mean value is 0 and standard deviation 7·5 approximately. Since the mean value of −3·9 is not significantly different from 0 ($0·5 < P < 0·10$), the 20 patients had attained the euthyroid state as assessed by the B.M.R. criterion. At the beginning of treatment using potassium perchlorate the mean of the initial readings of B.M.R.s for the 20 patients was +35·7; at the conclusion or rather at 0·35 week before " cure " the mean value was 0·0, with a standard deviation of 10·6. Thus once again the

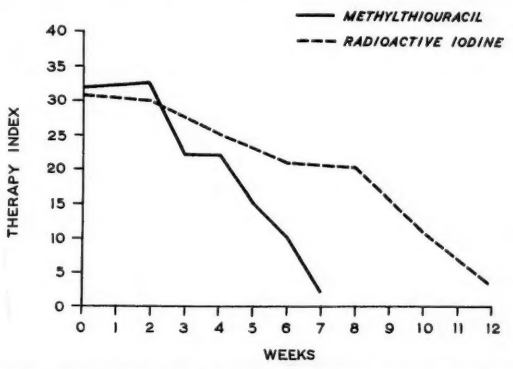

Fig. 3—Rate of change of the therapy index produced by methylthiouracil and by radioactive iodine.

TABLE IV—TIMES TAKEN TO EFFECT " CURE " IN PATIENTS WHO RELAPSED AFTER TREATMENT. SERIES 2.

Patient no.	Time to effect " cure " (weeks)		Difference (weeks)	Patient no.	Time to effect " cure " (weeks)		Difference (weeks)
	Methylthiouracil initial therapy	Potassium perchlorate retreatment			Potassium perchlorate initial therapy	Methylthiouracil retreatment	
21	9	12	−3	7	18	10	+8
22	10	10	0	9	14	7	+7
23	9	22	−13	10	11	9	+2
24	11	9	+2	11	7	4	+3
25	15	22	−7	13	13	14	−1
26	10	12	−2	14	9	4	+5
27	7	16	−9	..	..	..	..
33	6	6	0	..	..	..	..
Mean time to " cure "	9·6	13·6	−4·0		12·0	8·0	+4·0

estimation of the B.M.R. confirmed that patients had attained the euthyroid state.

Series 2 (" Cross-over " Observations)

In series 2 the time taken to effect " cure " in 8 subjects who initially received methylthiouracil and who, after recurrence of the disease were given potassium perchlorate, are shown in table IV. " Cure " was also confirmed by B.M.R. estimations in this group of subjects.

A t-test shows that the difference of 4 weeks is not significantly different from zero ($t=-2{\cdot}18$, $0{\cdot}05<P<0{\cdot}10$). It should, however, be noted that the difference found—i.e., that potassium perchlorate took 4 weeks longer than methylthiouracil for " cure " to be obtained in the same patients—is similar to the difference found in series 1 in which different patients were given the two drugs. In 6 subjects who had received potassium perchlorate and who were given methylthiouracil after recurrence of the disease, the times to " cure ", confirmed by B.M.R.s, are also shown in table IV. A t-test shows that in this group of subjects the difference of 4 weeks is significantly different from zero ($t=-2{\cdot}93$, $P<0{\cdot}05$). Again the slower rate of control by perchlorate is similar to that obtained between the two groups of 20 patients in series 1.

The findings in these two " cross-over " tests show that it does not matter which drug is given first. It is valid therefore to consider both " cross-over " tests together and to conclude that in this group of 14 subjects potassium perchlorate in the doses used took 4 weeks longer than methylthiouracil to control the disease. These observations confirm the results of series 1 and provide evidence that the method of assessment is reproducible. They also show that the " cross-over " type of control is unnecessary and that no fallacy has arisen from the method of using alternate cases for the two drugs.

Comparison of the Response to Antithyroid Drugs and Radioactive Iodine

The therapy index can be used to compare the response to antithyroid drugs with other forms of treatment—e.g., radioactive iodine. Fig. 3 illustrates the rate of response in one patient treated with 7 mC. of radioactive iodine compared with the patient shown in fig. 1A treated with methylthiouracil. We are now using the method to study the therapeutic response of a group of patients who have been treated with radioactive iodine.

Discussion

There are many advantages in being able to follow quantitatively the degree of improvement which results from therapeutic procedures, and the purely clinical method we describe here makes it possible to obtain more consistent estimates of a patient's progress than when conventional methods are used. Thus when it is necessary for the same patient to be seen from time to time by different clinicians, our system of scoring tends to eliminate personal bias in the interpretation of the observations. The proforma also acts as an aide-memoire enabling facts to be recorded and analysed quickly. It should be stressed that in systems of this type it is necessary to use a standard method of history-taking and to adopt rigid criteria for the recognition of physical signs. Used as a method of scientific investigation our scheme enables statistical methods to be applied to the results of treatment. In the present study for example, it has enabled us to show that the usual therapeutic response to antithyroid drugs is linear with time. It has also brought out the absence of any relationship between the initial severity of the disease and the rate of therapeutic response.

We feel, however, that the main value of this method of assessment is to provide a more accurate method of comparing the therapeutic effectiveness of different antithyroid compounds. There are comparatively few ways in which this can be done. In animals, methods depending on their goitrogenic action have been devised using either the immature rate (Astwood et al. 1945) or the chick (VanderLaan and Bissell 1946). In man, Stanley and Astwood (1947) have shown that the property which some antithyroid drugs possess of inhibiting the uptake of radioactive iodine can be utilised to give a measure of their relative potencies. Though this technique has the great merit that the comparison is made in the human subject, it is known that the results are not necessarily applicable to a patient suffering from thyrotoxicosis. Moreover, it is valid only when applied to drugs which act at the same point on the chain of thyroid-hormone synthesis and so cannot be used to compare the activity of drugs such as potassium perchlorate with the thiouracils and imidazoles since the former act on the iodide-trapping mechanism whereas the latter affect the conversion of iodide to organically bound iodine.

Drugs should, if possible, be assayed on patients suffering from the disease for which they are to be used, so that the pharmacological mechanisms underlying their effect becomes relatively unimportant. For this reason we believe that the ratio between the effectiveness of methylthiouracil and potassium perchlorate in the doses we chose is the most accurate figure so far recorded. It is of great interest, and provides strong confirmatory evidence of the validity of our method, that an almost identical difference in activity was shown in two separate experiments of different design. In both series of cases the conclusions were confirmed by estimation of B.M.R. In the second series each patient acted as her own control and the method used is an application to man of the " cross-over " tests used in animals by experimental pharmacologists. So far as we know this is the first example of the use of this particular technique in human pharmacological investigations. There are, of course, few conditions in which it is permissible to stop the administration of an effective drug and to allow the patient to relapse before using a second form of treatment. These observations also showed that the order of administration of the two antithyroid drugs did not affect the final result.

We believe that this scoring system of assessing therapeutic response in thyrotoxicosis is widely applicable. We have described in this paper how it can be used to compare the activities of two antithyroid drugs. The doses we used were those which we were using when the tests were begun, and the results indicate that, weight for weight, methylthiouracil is more potent than potassium perchlorate. Further observations, which will be the subject of a separate communication, show that this is a question of dosage, and that in higher doses potassium perchlorate is an equally effective form of treatment.

Summary

A clinical method of comparing the relative effectiveness of therapeutic procedures in thyrotoxicosis is described. It is based on the allocation of numerical values to those features of thyrotoxicosis which can be reversed by treatment. The sum of these values is called the therapy index and can be used to assess the progress of an individual case. We illustrate its use in the comparison of two antithyroid drugs. Thus therapy indices were recorded weekly in two groups of 20 cases, one group receiving methyl-

thiouracil and the other potassium perchlorate. The antithyroid activity of both drugs was assessed by the time taken for the index to fall within the range 0 to 5. Estimations of the basal metabolic-rate confirmed that at this level patients were euthyroid. The time taken to reach the euthyroid state was independent of the initial severity of the disease. In 33 of 40 patients the rate of therapeutic response bore a linear relationship to time. Methylthiouracil in doses of 600 mg. a day for three weeks followed by doses of 300 mg. a day was shown to be a more effective antithyroid drug than potassium perchlorate in doses of 600 mg. a day. A " cross-over " test carried out on 14 patients, who had relapsed after a first course of treatment, confirmed this conclusion.

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A COMPARISON OF POTASSIUM PERCHLORATE, METHYLTHIOURACIL, AND CARBIMAZOLE IN THE TREATMENT OF THYROTOXICOSIS

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AT some time during the course of their disease the majority of patients with thyrotoxicosis receive an antithyroid drug. It is probable that these substances provide the most satisfactory form of treatment for most young patients and the speed and certainty of their action often make their immediate administration necessary even when it has been decided subsequently to use an alternative form of treatment. It is obviously of importance to know which is the most effective and the safest member of the group. The ideal antithyroid drug should be rapid in its action and should produce no adverse side-effects. In this country the two most commonly used drugs are methylthiouracil and carbimazole. In other countries propylthiouracil and methimazole are popular. All, however, occasionally produce toxic effects, of which agranulocytosis is the most serious since it may prove fatal. The most common adverse reaction is the drug rash, but nausea, drug fever, aplastic anæmia, thrombocytopenia, conjunctivitis, and lymph-gland enlargement have all been reported.

Methylthiouracil was first introduced in 1944 and was for long the standard antithyroid substance in use in this country. Carbimazole received favourable reports in 1953 from Doniach and from Poate. It was said to produce fewer side-effects than methylthiouracil although its action was slower. Its use has tended to increase especially since evidence that it is less toxic was produced by Greene and Morgan (1956) and by Burrell et al. (1956). It is said to be ten times as active as methylthiouracil and is usually given in one-tenth of the dose. The *British Pharmacopœia* recommends that the controlling dose of methylthiouracil should be from 0·2 to 0·6 g. daily and of carbimazole from 30 to 60 mg. daily.

Potassium perchlorate is a rival and more recent antithyroid drug with a different type of action. Unlike the thiouracils and imidazoles which prevent the iodination of tyrosine, it acts by inhibiting the iodide-trapping mechanism of the thyroid gland. As a simple inorganic compound it would seem a priori to be less likely to produce sensitisation effects than the organic antithyroid substances, and in particular to be less likely to damage the hæmopoietic system. It was first shown to be a suitable substance for clinical use by Godley and Stanbury (1954). This was confirmed in a much larger series of cases by Morgans and Trotter (1954) who found that the rate of response produced by 400 mg. daily was less than that produced by methylthiouracil in a dose of 200 mg. daily.

Shortly after their report was published we decided to assess the relative merits of potassium perchlorate, methylthiouracil, and carbimazole. We shall present our conclusions based on a study of more than 450 patients. It soon, however, became evident that while the comparative incidence of the side-effects of these substances would be revealed by this investigation a comparison of their relative efficacy presented a more difficult problem. For this reason we devised a clinical method of comparing antithyroid drugs based on the allocation of points to those features of thyrotoxicosis which are reversible by therapeutic measures. This enabled us to derive a " therapy index " which could be followed from week to week and the time taken for it to reach and remain at a value of 5 or lower could be used as a measure of the effectiveness of the form of treatment. We have already recorded in illustration of our method a comparison of the effect of 600 mg. daily of potassium perchlorate with that of methylthiouracil in doses of 600 mg. daily for two weeks followed by 300 mg. daily. Using these dosage schemes methylthiouracil was more effective (Crooks et al. 1960). It seemed to us probable that this result depended on the relative doses used and a further series of cases has been studied using 1000 mg. of potassium perchlorate daily. Since our clinical experience had led us to doubt the statement that carbimazole is, weight for weight, ten times as active as methylthiouracil we also compared these two substances.

Potassium perchlorate proved to be both effective and relatively free from side-effects and we now use it routinely. We have, therefore, studied more closely some of its alleged disadvantages notably the tendency for its activity to be affected by variations in the dietary intake of iodine and its liability when used before operation to produce an unduly vascular gland. We also report the results of its use in pregnant patients with thyrotoxicosis.

Material and Methods

We have studied two further groups of 20 cases in addition to the two already reported (Crooks et al. 1960).

All the patients had diffuse goitres and exophthalmos and thus were examples of classical Graves's disease. To one group carbimazole was given in doses of 20 mg. three times a day for two weeks followed by 10 mg. three times a day (i.e., one-tenth of the dose of methylthiouracil which was used in our previous series). Potassium perchlorate was given to the other group in a dose of 200 mg. 5 times a day. The dietary intake of iodide was not restricted.

The method of comparison was that used in the earlier series except that estimations of basal metabolic-rate (B.M.R.) were made only at the end of the investigation to confirm that the patients were euthyroid.

TABLE I—DISTRIBUTION OF PATIENTS IN SERIES 3 RECEIVING CARBIMAZOLE AND POTASSIUM PERCHLORATE (1000 MG. DAILY) SHOWING TIME TAKEN TO EFFECT " CURE "

Time to effect " cure " (weeks)	Carbimazole (no. of patients)	Potassium perchlorate (1000 mg. daily) (no. of patients)
3–4	..	..
5–6	..	8
7–8	7	3
9–10	2	4
11–12	4	1
13–14	3	2
15–16	..	1
17–18	2	..
19–20	..	1
21–22	2	..
Total	20	20
Mean time to " cure "	12·3 weeks	9·4 weeks

The study of the comparative toxic effects of these substances is based on observations made on 486 patients seen and treated by us in our wards or clinic. After reference to their general practitioner they continued to attend hospital from time to time so that the occurrence of toxic effects could be accurately recorded.

Results

" *Therapy Indices* "

The times taken to effect " cure " for both drugs are shown in table I. The mean time to " cure " of the 20 patients on carbimazole was 12·3 weeks and the corresponding figure for potassium perchlorate was 9·4 weeks.

Table II gives the mean times to " cure " of the groups treated with methylthiouracil, carbimazole, and potassium perchlorate in doses of both 600 mg. and 1000 mg. daily.

For the purpose of statistical analysis the drugs have been represented by the letters A, B, C, and D as shown in the table. An analysis of variance on the 80 patients studied shows that there are significant differences between the mean values for A, B, C, and D. In particular A is significantly different from B and C ($P<0.05$); D is significantly different from B and C ($P<0.05$); and there was no significant difference between A and D. A further analysis of variance was carried out on the 60 patients remaining after the exclusion of those who had been given methylthiouracil. It was found that there was a significant difference between B and D ($P<0.05$); a significant difference between C and D ($P<0.05$); and no significant difference between B and C.

TABLE II—MEAN TIMES TO EFFECT " CURE " FOR METHYLTHIOURACIL, POTASSIUM PERCHLORATE, AND CARBIMAZONE

	Drug	Time to effect " cure " (weeks)
A	Methylthiouracil	9·1
B	Potassium perchlorate (600 mg. daily) ..	13·1
C	Carbimazole	12·3
D	Potassium perchlorate (1000 mg. daily) ..	9·4

These results can be summarised as follows: methylthiouracil in doses of 600 mg. daily for 2 weeks followed by 300 mg. daily and potassium perchlorate (1000 mg. daily) were equally effective as measured by the time taken to effect " cure ", while both were more effective than carbimazole in one-tenth of the dose of methylthiouracil or potassium perchlorate (600 mg. daily).

Effect of Variations in the Intake of Iodine on Potassium Perchlorate Therapy

Potassium perchlorate affects the iodide-trapping mechanism of the thyroid and it is known that the goitrogenic action of substances with this action can be overcome if sufficient iodide is given (Franklin et al. 1944). In our earlier series we advised patients given potassium perchlorate 600 mg. daily, to restrict their iodine intake by excluding fish from the diet, by using uniodised salt, and by avoiding medicines.

Diet histories from 8 patients and urinary assays from 20 patients revealed a great variation in the degree to which iodide restriction had been achieved. The therapeutic responses to potassium perchlorate of patients with relatively high and low intakes were statistically analysed and no difference was found. In our later observations therefore we have urged no dietetic restrictions and have merely advised patients to avoid certain cough medicines which contain iodide in relatively large quantities.

Preoperative Use of Potassium Perchlorate

It is generally agreed that antithyroid drugs should be used to prepare a thyrotoxic patient for partial thyroidectomy. The usual method is to bring the disease under control with one of the organic antithyroid drugs and then to give iodide for 10–14 days before operation. It is said that this renders the gland less vascular and diminishes the likelihood of postoperative thyroid crises.

Godley and Stanbury (1954) prepared 13 patients for operation with potassium perchlorate and stated that the consensus of opinion of the operating surgeons was that a few of the glands were more vascular than those of patients prepared with propylthiouracil and iodine. 2 patients who before operation received iodide in addition to perchlorate escaped from control. For this reason Morgans and Trotter (1954) did not use perchlorate in those patients who were likely to require partial thyroidectomy.

We have prepared 20 patients for operation with potassium perchlorate alone. 18 of these patients had small nodular glands and the surgeon did not find more technical difficulty due to increased vascularity of the gland than after conventional preparation.

Opinions as to the degree of vascularity must of necessity be highly subjective. It may well be that contradictory views on the effects of the antithyroid drugs on vascularity are due to variation in the selection of cases and to the lack of an investigation designed so as to eliminate the effects both of biological variation and of bias on the part of the surgeon. The blocking effect of potassium perchlorate on thyroid hormone synthesis continues for some time after the drug has been withdrawn and administration can cease at the time of operation.

Use of Potassium Perchlorate During Pregnancy

Opinion is almost unanimous that the most appropriate form of therapy for women who develop thyrotoxicosis during pregnancy is the administration of an antithyroid drug. Goitre and hypothyroidism have been reported in the infants of mothers who have received these substances but it is rare, and when it occurs the dosage has almost always been unduly high (Macgregor and Goodwin 1953). We have treated 12 pregnant thyrotoxic patients with potassium perchlorate and in each have achieved satisfactory control of the disease. One of the infants had a very slight enlargement of the thyroid gland which disappeared within 6 weeks. The remainder showed no abnormality of any kind. We report these results to show that the different mode of action of potassium perchlorate and its special physical properties do not render it more liable to affect the fœtal thyroid than the antithyroid substances in more common use.

Toxic Effects of Antithyroid Drugs

We have treated 486 patients with either methylthiouracil, carbimazole, or potassium perchlorate for sufficiently long to be able to assess their relative tendency to give rise to toxic side effects. Table III shows our results. No statistically significant difference was found

TABLE III—TOXIC EFFECTS

Toxic effect	Methylthiouracil (600 mg. daily 2 wks., then 300 mg. daily)	Carbimazole (60 mg. daily 2 wks., then 30 mg. daily)	Potassium perchlorate	
			600 mg.* or 1000 mg.	1500 mg.† or 2000 mg.
No. of cases	151	85	200	50
Skin rashes	5	4	1	5
Nausea	..	1	3	2
Drug fever	2	..	..	..
Agranulocytosis	2	2	..	1
Thrombocytopenia	1	..	..	..

* 35 patients. † 10 patients.

between the liability of the organic substances to produce sensitisation reactions such as skin rashes or blood dyscrasias. Potassium perchlorate, on the other hand, in doses of 1000 mg. a day or under was less likely than the organic antithyroid compounds to produce adverse effects of this type. Higher doses of potassium perchlorate produced reactions as frequently as the organic compounds.

The rashes produced by potassium perchlorate were maculopapular and were confined to the extremities except in 1 patient in whom the rash was generalised. This patient had an associated pyrexia and marked desquamation followed the disappearance of the eruption. In 3 of the 6 cases the rash subsided although the administration of the drug was continued.

The patient with agranulocytosis was a young woman receiving 1500 mg. of potassium perchlorate a day. During the third week of treatment she developed a sore throat, pyrexia, and generalised muscular pain. Blood examination showed a total polymorphonuclear leucocyte count of 750 per c.mm. The peripheral blood was otherwise normal and the bone-marrow showed no evidence of a maturation defect of the white-cell series. Administration of the drug was stopped and the leucocyte count rose rapidly to normal levels. The patient had received no other drugs which might have caused leucopenia.

The rashes produced by the organic antithyroid compounds were all maculopapular. This is a type of eruption which is well known to occur in those who become sensitised to this series of compounds. Urticaria which has also been reported was not observed in this series.

4 patients complained of nausea while taking potassium perchlorate. 3 of them were able to continue taking the drug when an antacid mixture was given along with it and the nausea disappeared within a week. The fourth refused further treatment.

Discussion

The " therapy index " has been used to assess the rate of improvement in four different groups of patients suffering from classical Graves' disease. One group received carbimazole, one methylthiouracil, and the other groups potassium perchlorate in two different doses. From these investigations we are able to draw two conclusions. First, carbimazole is less effective than methylthiouracil when given in one-tenth of the dose. Secondly, potassium perchlorate is more effective in high than in low dosage.

The very extensive literature on the antithyroid drugs is fully reviewed by McGavack (1951), Werner (1955), and Crooks (1957), and it is clear that the four drugs most widely used at present are methylthiouracil, propylthiouracil, methimazole, and carbimazole. All are effective and relatively safe. The particular substance used by any given physician seems to be determined by two factors. In the first place it is clear that the country of origin is important since methylthiouracil and carbimazole were both first synthesised and marketed in Europe whereas propylthiouracil and methimazole were originally American products. The second factor of importance is the relative conservatism of the individual clinician. Most physicians see no reason to try a new remedy if the existing one is satisfactory although some are impressed by new substances even if their advantages are marginal. Moreover, any clinician tends to be overimpressed by an example of a patient under his care who shows a serious side-effect even though the statistical hazards of this occurrence can be shown to be small. Against this background of national and individual prejudice there is almost no statement which has not been made about the relative effectiveness, speed of action, and toxicity of these drugs.

We have found no published observations on the relative dosage of antithyroid drugs which cannot be explained on the view that the response of a patient to an antithyroid drug is a function of the dose. At a certain critical level a dose is reached at which synthesis of the thyroid hormone is completely blocked. Inspection of curves showing the effect of different doses of methylthiouracil on the uptake of radioactive iodine by the gland, as reported, for example, by Goodwin et al. (1949), illustrate this phenomenon.

The first problem in dealing with the dose of an antithyroid drug is to discover the least dose which in the majority of patients will effectively block secretion of the thyroid hormone during each 24 hours. This is probably of the order of 450 mg. for methylthiouracil, 60 mg. for carbimazole, and 1000 mg. for potassium perchlorate. The question then arises of the relative liability of these drugs to produce toxic side-effects. In spite of their importance we know relatively little about sensitisation reactions to drugs. It is not possible, for example, to say with certainty whether they are dependent on dose. With some drugs (e.g., amidopyrine) a single dose may produce a reaction in a sensitised patient. With others, such as chloramphenicol or the sulphonamides, there seems to be a tendency for reactions to be related to total dosage. In the case of the antithyroid substances the balance of evidence seems to suggest that they belong to the latter type (Lehr 1948). Certainly our own results show that potassium perchlorate produces more reactions in high than in low dosage. It seems therefore to us that it is unjustifiable to group together series of cases collected from the literature without allowing for this factor of dosage and without applying statistical tests of significance to all the results reported. The two published comparisons of carbimazole and methylthiouracil (Burrell et al. 1956, Greene and Morgan 1956) are thus rendered inconclusive.

Our tentative conclusions are these. There is no convincing evidence that any of the organic antithyroid drugs is significantly more toxic than any other when it is given in therapeutically equivalent dosage. Our experience suggests that potassium perchlorate is less liable to give rise to skin rashes or blood dyscrasias in doses which act as quickly as the conventional therapeutic doses of methylthiouracil and carbimazole.

Potassium perchlorate thus appears to us to be the antithyroid drug of choice. A few observers other than Godley and Stanbury (1954) and Morgans and Trotter (1954) have used it and found it satisfactory. Thus Kleinsorg and Krüskemper (1957) treated 47 cases with doses of 1·6 to 2·0 g. a day; 2 patients developed a rash. Buttaro and Brunori (1955) reported 25 patients successfully treated with doses of 600 mg. a day and 1 developed a skin rash. Observations in our series showed that it is

unnecessary to restrict the dietetic intake of iodine during the administration of potassium perchlorate. In our experience this drug can be satisfactorily used for pre-operative preparation when the gland is small and nodular. Whether or not it can be used in this way when the gland is large requires further investigation.

Sensitisation to potassium perchlorate can occur. The usual manifestation is a rash which usually subsides quickly even if administration is continued. It is much more likely to develop when the dosage is high. Our single case of agranulocytosis occurred in a patient receiving large doses of the drug but if the use of potassium perchlorate increases we should not be surprised to learn that this serious condition may be associated with lower doses or that the bone-marrow may be affected in other ways. The balance of present evidence, however, is in favour of its very low toxicity. It has the additional merit of being very cheap and it is of some interest that the only proprietary preparation of potassium perchlorate was for many years in category 5 of the List of Proprietary Medicines Classified by the Joint Committee on Prescribing which is published jointly by the Ministry of Health and the Department of Health for Scotland.

Summary

A clinical method of assessing the rate of improvement of groups of patients suffering from thyrotoxicosis has been applied to four series of cases receiving respectively methylthiouracil, carbimazole, and potassium perchlorate in two different doses. Carbimazole was less effective than methylthiouracil when given in one-tenth of the dose. Potassium perchlorate in high dosage was as effective as methylthiouracil and more effective than carbimazole and smaller doses of perchlorate.

Four larger series of patients receiving these drugs were studied to ascertain the incidence of toxic side-effects. Potassium perchlorate in a daily dose of 600–1000 mg. produced fewer side-effects than when it was given in daily doses of 1·5–2·0 g. The lower dosage range also gave rise to fewer side-effects than either methylthiouracil or carbimazole in therapeutically equivalent doses. No statistical difference in the incidence of sensitisation reactions was found between the latter two substances.

Potassium perchlorate in high doses is liable to produce skin rashes, and in 1 of our cases agranulocytosis developed.

It is not necessary to restrict the dietary intake of iodine during perchlorate administration. It can be used to prepare patients for thyroidectomy when the gland is small and nodular and can also be used during pregnancy. Potassium perchlorate, 1000 mg. daily in divided doses, is the antithyroid drug of choice in the medical treatment of thyrotoxicosis.

We wish to thank Dr. R. A. Robb, Mitchell lecturer in statistics, University of Glasgow, for help with the statistical aspects of this work, and Mr. D. H. Clark, F.R.C.S., who carried out the thyroidectomies to which we refer.

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THE INCREASE IN DIFFUSING CAPACITY OF THE LUNGS ON EXERCISE

AN EXPERIMENTAL AND CLINICAL STUDY

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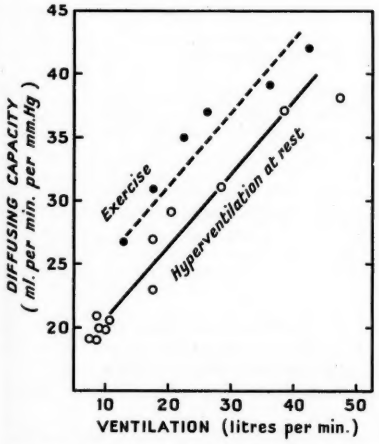
WHEN oxygen is taken up from the alveoli of the lungs it has to penetrate the mechanical barrier of the tissue elements and fluids separating it from the molecules of hæmoglobin in the red cells; the process is one of simple physical diffusion. Methods of measuring the permeability of this barrier to gases have been elaborated which permit an estimate of the so-called *diffusing capacity* of the lungs. The simplest of these uses carbon monoxide as the test gas, and measures its rate of absorption in the steady state (Bates, Boucot, and Dormer 1955). The measured rate of uptake of this gas in low concentration in an inspired gas mixture is divided by its mean alveolar concentration during the test (expressed as partial pressure) to give a result in ml. per min. per mm. Hg. On physical principles, it may be assumed that the diffusing capacity thus measured is proportional to the area of the diffusing surface and varies inversely with its thickness. Normal results vary between 15 and 25 ml. per min. per mm. Hg at rest and from 25 to 40 ml. during exercise. Experience in the past few years in many centres has shown how valuable measurements of diffusing capacity are clinically; moreover, many facts of physiological interest and importance have been revealed by them. Among the latter is the observation, repeatedly confirmed, that the diffusing capacity is greatly increased during exercise. The object of this communication is to report some investigations which throw light on the way in which this change is brought about.

Investigations and Conclusions

In an experimental assessment of the steady-state method of measuring pulmonary diffusing capacity using carbon monoxide (MacNamara, Prime, and Sinclair 1959) we drew attention to the fact that the results obtained were significantly dependent on the minute-volume of respiration during the test. This finding made us wonder whether the apparent increase in diffusing capacity on exercise was due entirely to the effects of hyperventilation. We therefore measured the diffusing capacity in four healthy subjects at rest during voluntary hyperventilation at various rates. We found that the diffusing capacity rose steadily with increasing ventilation, showing no definite tendency to a maximum value within the range of voluntary hyperventilation which it was possible to maintain for the time required for the test. These results were compared with values of diffusing capacity in the same subjects, measured at various rates of exercise, by plotting both sets of values on a graph relating them to pulmonary ventilation. Contrary to our expectation, we found that the curves plotted from the exercise values did not coincide with those for voluntary hyperventilation but lay above them. A typical comparison in one subject is shown in the figure. This discovery has since been confirmed by results published by two groups working

independently in America (Ross, Frayser, and Hickham 1958, and Turino, Brandfonbrener, and Fishman 1959).

We concluded that some factor other than hyperventilation contributed to the increase occurring during exercise and that this was most likely to be the consequence of the increased pulmonary blood-flow. Before proceeding further we excluded, by suitable experiments, the possibility that our findings were the result of sampling errors or changes in mean lung volumes (see appendix). We then considered how best to assess the effects of increasing pulmonary blood-flow and decided as a first step to measure diffusing capacity in a number of patients with congenital heart-disease without pulmonary hypertension, in whom pulmonary blood-flow had been measured by cardiac catheterisation and found to be above normal. The data collected from these patients are set out in the table. We found that in all of them diffusing capacity was above normal at rest, but was not increased beyond normal on moderate exercise; in other words, the range of change observed between rest and exercise was not so great as in normal subjects, although the minute-volume of respiration increased in a normal manner.



Plot of values of D_L during hyperventilation at rest (o) and during periods of exercise of differing severity (●) in one subject.

No mention has yet been made of similar findings by other workers. Ross et al. were unable to demonstrate any increase in diffusing capacity at rest when cardiac output was increased as much as twofold by administration of atropine or noradrenaline to normal subjects, whilst Turino et al. failed to find results below normal in subjects with a low cardiac output due to mitral stenosis.

The findings described suggest very strongly that the increase in diffusing capacity accompanying exercise is in large part mediated by the hyperventilation that exercise induces. Voluntary hyperventilation probably increases the area of the capillary wall separating blood and gas, either by actually distending the pulmonary capillaries with blood or by causing alveoli which are more or less functionless during quiet breathing to become ventilated and perfused. The high diffusing capacity observed in the patients suffering from atrial septal defect is likewise due probably to an increase in pulmonary alveolar-capillary blood volume with a consequent increase in area of the interface between blood and gas. The most likely reason for the failure to detect any change in diffusing capacity when pulmonary blood-flow is increased by drugs (Ross et al. 1958) is that these substances had no effect on pulmonary capillary blood volume; pulmonary blood-flow per se would be expected to have no effect on the rate of carbon-monoxide uptake from the alveolar gas.

The possibility should be mentioned that hyperventilation in the absence of exercise may produce values for diffusing capacity which are lower than they should be because a high alveolar oxygen tension depresses the rate of uptake of carbon monoxide by hæmoglobin. During hyperventilation at rest alveolar oxygen tension may rise as high as 125 mm. Hg which is about 30 mm. Hg higher than that found during heavy exercise. Calculation from data published by McNeil, Rankin, and Foster (1958) shows that this difference could depress the pulmonary diffusing capacity by about 2 ml. per min. per mm. Hg during voluntary hyperventilation. This estimate represents the highest possible effect of the difference in alveolar oxygen tension in these two states; in most of our experiments exercise was not very severe and was not probably accompanied by a fall of alveolar oxygen tension below about 100 mm. Hg. Thus it is possible that about half the observed difference in level between the results on exercise and those during voluntary hyperventilation may be due to this effect.

We therefore conclude that the observed increase in pulmonary diffusing capacity during exercise is due primarily to an increase in the area of capillary wall exposed to alveolar gas. This is mediated partly by the hyperventilation itself and partly by the increased cardiac output in exercise.

PULMONARY DIFFUSING CAPACITY FOR CARBON MONOXIDE (D_L) MEASURED BY THE STEADY-STATE TECHNIQUE AT REST AND DURING EXERCISE IN 10 PATIENTS SUFFERING FROM AURICULAR SEPTAL DEFECT WITH HIGH PULMONARY BLOOD-FLOW (CO) BUT NO INCREASE IN PULMONARY VASCULAR RESISTANCE

Expected values for D_L at rest are shown in parentheses; they are derived from values obtained in healthy subjects of the same height and weight.

Patient	Age and sex	Height (in.)	Weight (lb.)	Pulmonary ventilation (litres per min.)		D_L (ml. per min. per mm. Hg		CO (l per min.) at rest
				Rest	Exercise	Rest	Exercise	
1	14 F	..	..	11·2	27·7	25 (..)	29	22
2	15 M	60	99	7·7	22·9	33 (15)	36	15
3	16 M	62	112	9·4	19·6	29 (17)	33	8
4	17 F	68	118	7·1	18·9	28 (20)	33	19
5	18 M	64	113	7·8	20·8	37 (19)	46	14
6	36 M	66	122	6·3	27·5	24 (20)	39	13
7	36 F	..	..	10·0	29·0	27 (..)	40	23
8	45 F	64	126	14·0	..	32 (20)	..	30
9	46 M	70	140	12·0	28·3	31 (23)	34	22
10	46 M	66	136	9·8	25·6	33 (22)	40	15

Summary

In patients suffering from atrial septal defect with high pulmonary blood-flow but without pulmonary hypertension the pulmonary diffusing capacity is considerably higher than normal; exercise increases it relatively less than in normal subjects. This indicates that the area of blood-gas interface is the important factor underlying the increase in diffusing capacity which occurs in normal subjects during exercise and during voluntary hyperventilation.

Appendix

Pulmonary diffusing capacity (D_L) was measured in these experiments by a method similar to that of Bates et al. (1955) fully described by MacNamara et al. (1959).

1. We excluded errors of sampling as a cause of the increase in D_L observed during voluntary hyperventilation by taking our alveolar samples simultaneously at two points in expiration separated by 450 ml. of expired gas. When tidal volumes were of the order of 1 litre and over, little difference was found between these samples.

2. That the observed change was not solely due to large swings in intrathoracic pressure we confirmed by constricting the airway of the apparatus while the subject maintained a normal rate and depth of breathing. This procedure did not alter the value of D_L, although respiratory pressure swings of 40–50 cm. of water were induced which are of the same order as those encountered during vigorous hyperventilation with a free airway.

3. We carried out the tests with the subjects breathing with their chests voluntarily held above the resting respiratory position so that the volume of gas contained by the lungs at the end of each breath was up to 21 above normal. This manœuvre had no effect on the diffusing capacity, confirming Marshall's previous findings (Marshall 1958).

4. Finally we arranged our apparatus so that the subjects hyperventilated against a constant positive pressure of about 15 cm. of water; the object of this manœuvre was to drive blood out of the lungs and thus, on our hypothesis outlined above, to prevent or limit the expected increase in D_L. This experiment failed to achieve its object, probably because the pressure used was too low; pressures higher than this could not be tolerated long enough for the tests.

Our thanks are due to Dr. J. G. Scadding and our laboratory staff who have helped us considerably in the production of this work.

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TRANSTHORACIC VAGOTOMY FOR STOMAL ULCERATION

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STOMAL ulceration following gastric resection is not common, while stomal ulceration following gastroenterostomy is seen only as an occasional legacy of the past. Both these groups of cases can be treated by gastric resection with excision of the ulcer, which may or may not include an abdominal vagotomy. Abdominal vagotomy alone, as a planned procedure, may prove very difficult; and, whether it be difficult or easy, the surgeon may be tempted to change his plan and resect an ulcer mass that would be better left alone. Transthoracic vagotomy, as the sole procedure, is an alternative which offers certain definite advantages such as technical ease, very low morbidity and mortality rates, and freedom from the sequelæ of extensive excision of the stomach. We describe here our results with this procedure.

Last April we reviewed all the cases of stomal ulceration seen on the professorial unit at the Liverpool Royal Infirmary between December, 1952, and mid-1957 and treated solely by transthoracic vagotomy. All but a few were personally questioned and examined. 2 remain untraced (a common experience in a seaport town), leaving for assessment 23 (17 males, 6 females), the youngest of whom was 28 and the oldest 73 at the time of operation.

Barium-meal examination had provided definite evidence of ulceration in 12 cases and suggestive evidence in 4. In the remaining 7 there were strong clinical grounds (severe epigastric pain, vomiting and/or bleeding) for the diagnosis of stomal ulceration. Gastroscopy was carried out in some cases, but gave little help. Fractional test-meal was performed in most cases, provided supportive evidence in 11 where high or average acid levels were found. Negative findings in test meals after gastric operations are notoriously unhelpful. We have not used the insulin-provoked test meal for gastric acidity after vagotomy. Today the twelve-hour overnight secretion would ordinarily be estimated, but this was not done routinely in our series.

TABLE I—RESULTS OF TRANSTHORACIC VAGOTOMY FOR STOMAL ULCERATION

Previous operation	No. of cases	Failures
1. Gastro-enterostomy	4	0
2. Gastric resection:		
Polya	5	0
Steinberg [1]	2	1
Roux-Y	4	1
Billroth I (including modified [2] Billroth I)	5	2
Moroney [3]	3	2

1. Double-lumen gastrojejunal anastomosis of the " pantaloon " type.
2. End-to-side gastroduodenal anastomosis with wide stoma.
3. Colonic implant between stomach and duodenum with reversed peristalsis.

No deaths had resulted from the operation nor any major complications. While in hospital some patients had had segmental left-lower-lobe collapse with a small effusion, and for a few months after operation a minority complained of wound pain.

Results

The results are summarised in table I.

Gastroenterostomy group (4 patients).—The stomal ulceration had developed fourteen to twenty-five years after gastroenterostomy. Vagotomy relieved all four patients of their ulcer symptoms and they were well at the time of follow-up.

Gastric-resection group (19 patients).—The majority had previously had more than one operation. In 13 all symptoms were removed by thoracic vagotomy and 11 of these were well at the time of follow-up. The other 2 had died from unrelated causes.

The first had developed stomal ulceration after a Steinberg gastrectomy and was relieved by vagotomy; but he died six years later from carcinoma of the bladder. The second, whose stomal ulcer followed a Billroth I gastrectomy for gastric ulcer, was also relieved by vagotomy but died of cirrhosis of the liver nine months after the operation.

Of the remaining 6 (unrelieved) cases, no fewer than 4 proved to have been badly selected. 1 patient, who had had a Roux-Y gastrectomy, was a chronic alcoholic and was afterwards admitted to a mental home. The other 3, who had complained of epigastric pain and vomiting, were found at subsequent laparotomy to have no evidence of stomal ulcer, active or healed. Their histories are:

CASE A (*Steinberg gastrectomy*).—1951: gastropexy elsewhere for partial gastric volvulus. 1952: Steinberg gastrectomy for duodenal ulcer and hiatus hernia. 1953: transthoracic vagotomy (confirmed histologically) failed to relieve persistent epigastric pain. 1958: no ulcer found at laparotomy. Converted to " Moroney ". Since then the attacks of epigastric pain have been less frequent; they seem to have been due to intestinal hurry.

CASE B (*modified Billroth I*).—1952: pylorectomy and vagotomy for duodenal ulcer, performed elsewhere. 1953: modified Billroth I for persistent duodenal ulcer. 1957: transthoracic vagotomy. On histological examination, amputation neuromata found. Symptoms unrelieved. Roux-Y conversion carried out as a last resort but without improvement.

CASE C (*Moroney*).—1926: gastroenterostomy. 1946–47: Polya gastrectomy for recurrent ulceration. Severe nutritional deficiencies followed (anæmia, pellagra, riboflavin deficiency) probably as a result of extreme intestinal hurry (barium was

demonstrated in the cæcum an hour after ingestion). 1952: Moroney conversion for intestinal hurry. 1953: transthoracic vagotomy for suspected stomal ulcer. 1956: Roux-Y conversion after excision of colonic implant (no ulcer found). Pain, vomiting, and nutritional deficiencies persist, albeit to a lesser extent. A recent barium meal was negative. Fasting test-meal showed achlorhydria.

In the 2 other patients stomal ulceration continued despite transthoracic vagotomy.

CASE D (*modified Billroth I*).—1953: Modified Billroth I, with abdominal vagotomy for duodenal ulcer. 1955: transthoracic vagotomy for a stomal ulcer (bilateral vagal-nerve section was confirmed on histological examination). 1957: insulin test-meal at blood-sugar 35 mg. per 100 ml. produced 100 clinical units of total acid. Further one-third gastric resection with Polya anastomosis for posterior stomal ulcer. Has since remained very well.

CASE E (*Moroney*).—1949: Polya gastrectomy elsewhere (apparently no ulcer was found). 1952: converted to Moroney for intractable dumping. Abdominal vagotomy. 1952: 6th–9th left intercostal nerves crushed for severe epigastric pain, without relief. 1953: transthoracic vagotomy (fractional test-meal showed hyperchlorhydria). Histological proof of bilateral vagotomy obtained. One week after operation, test-meal showed achlorhydria. 1957: radiography revealed stomal ulcer. Gastric acidity high. A large stomal ulcer was resected and the anastomosis converted to a Roux-Y type; an abdominal vagotomy was also done. The patient has since remained well.

Discussion

The numbers in this series are small, and in the disappointing cases there was an almost bewildering variety of antecedent procedures. Perhaps the most striking fact is that stomal ulceration following uncomplicated Polya gastrectomies (5 cases) or gastroenterostomy (4) was always completely relieved by transthoracic vagotomy.

Study of the literature suggests that, after gastrectomy, the operation of choice is vagotomy alone, which may be expected to relieve stomal ulceration in three cases out of every four (table II). Our figures support this view with 13 successes in 19 cases. Walters (1959) has suggested that stomal ulceration following gastroenterostomy is somewhat less favourably affected by vagotomy alone (table II) and that in these cases gastric resection is to be preferred. Gastric resection, however, is an operation with its own mortality and morbidity, and we have chosen to try the lesser procedure first. The fact that this succeeded in all 4 indicates that, if the gastroenterostomy is well placed and functioning satisfactorily, transthoracic vagotomy is a sound procedure.

TABLE II—PREVIOUSLY REPORTED RESULTS OF VAGOTOMY FOR STOMAL ULCER

Authors	Cases with previous gastro-enterostomy		Cases with previous gastric resection	
	No. of cases	No. of failures	No. of cases	No. of failures
Crile and Brown (1951)	18	3	13	0
Hand and Patey (1953)	2	1	2	0
Wells, B. W. (1954)	14	10	25	10
Walters, Chance, and Berkson (1955)	27	6	78	23
Osnes (1955-56)	5	3	10	0
Knox and West (1959)	5	3	20	3
Davey (1959)	1	0	17	3
Totals	72	26 (*36%*)	165	39 (*23·6%*)

On stomal ulcer after Roux-Y gastrectomy the literature is not informative. Some surgeons are at present performing an elective Roux-Y gastrectomy subtotally without vagotomy for duodenal ulcer, and a proportion of recurrences must surely be expected. A priori thoracic vagotomy should relieve such ulceration. Our own practice has been to employ vagotomy as a routine at the time of the gastrectomy or deliberately across the chest at the same or a second operation in cases of difficulty. Of a series of such operations (Wells and Johnston 1955) stomal ulceration has been suspected in only one. In that one case (which we have mentioned above) the diagnosis was neither confirmed nor disproved: the symptoms were not relieved, but the patient, a chronic alcoholic, has been admitted to a mental institution. Nothing can be deduced except that he was a bad subject for any operation.

Our two cases in which stomal ulceration persisted after thoracic vagotomy are of special interest. It is disturbing that, despite removal of the pyloric antrum and resection of the vagus nerves—attempted and apparently achieved from both below and above the diaphragm, and confirmed histologically—enough acid remained or recurred to provoke further ulceration. How this residual acid was produced remains in some doubt: we do not know whether resection of the nerves was incomplete, whether regeneration took place, or whether a hormonal factor was responsible. But the relapses did in fact occur, and in both cases the ulceration was then apparently relieved by a high gastric resection. This satisfactory end-result presumably excludes the possibility of their being examples of the Zollinger-Ellison syndrome. Possibly the initial antral resections went insufficiently high on the lesser curvature.

Conclusions

1. Transthoracic vagotomy is simple and safe.

2. It is probably the best means of treating stomal ulceration following otherwise uncomplicated gastrectomy, or following gastroenterostomy provided the stoma is well placed and functioning satisfactorily.

3. The diagnostic proof of stomal ulceration is not always easy. Estimation of night secretion, not routinely available at the time of this study, may prove invaluable. Persisting acid is a reasonable indication for vagotomy.

4. On a-priori grounds, vagotomy is necessary in operations of the Billroth I type for duodenal ulcer. If acidity persists after abdominal vagotomy, thoracic vagotomy should be undertaken as an adjuvant.

5. In patients who have undergone bizarre or multiple operations on the stomach and duodenum, accurate diagnosis may be difficult. The surgeon must weigh the dangers and complications of a further abdominal operation against the advantages of actually seeing the lesion. In the presence of pain suggestive of ulcer, and of continued night secretion of acid, thoracic vagotomy is safe and worth while.

6. In some late and complicated cases, disappointments are inevitable whatever is done. It is sententious and not really helpful to suggest that the solution lies in more careful selection in the first place.

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HYPOPITUITARY COMA AND PSYCHOSIS

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THIS case of hypopituitary coma followed by organic psychosis seems worthy of record because the coma was reversed dramatically by treatment and the patient recovered completely from the psychosis.

Case-report

A woman, aged 46, was admitted to the London Hospital [L.H. no. 018163] from the Emergency Bed Service on June 11, 1958, with a provisional diagnosis of meningitis.

10 years previously, after the birth of her third child whom she breast-fed for 3 days only, her menstrual periods had decreased from 3–4 to 1–2 days, and their frequency from 4 to 7–10 weeks. 5 years later, after appendicectomy, menstruation ceased completely. Her general health had deteriorated, and she had lost all libido. She felt the cold more, and noticed some thinning of her hair.

2 days before admission she felt faint on getting up from a hairdresser's chair, but was able to walk home. She went to bed, and in the evening felt feverish. Next morning her family practitioner found she had a pyrexia of 102°F, but no other abnormal physical signs. Later that day her doctor's deputy found her drowsy. The following day (June 11) she was stuporose, with neck stiffness.

Course in London Hospital

She was admitted at 3 P.M. on June 11. Her temperature was 101·6°F and her blood-pressure 105/60 mm. Hg. She was well nourished, and her skin was soft, pale, and dry. The hair on her head was soft and normal in distribution, but on her eyebrows and pubes it was scanty, and in the axillæ absent. She opened her eyes in response to her name, but she would not obey simple commands, and she resisted examination, responding violently to painful stimuli. She had head retraction, but Kernig's sign was negative. The central nervous system was otherwise normal. Respiration was irregular, and she yawned frequently. Some lymph-nodes in the left side of the neck were tender.

Lumbar puncture revealed clear cerebrospinal fluid (C.S.F.) under normal pressure, containing 10 lymphocytes per c.mm. and 40 mg. protein and 35 mg. sugar per 100 ml. The blood-sugar was 38 mg. per 100 ml., and the sodium, potassium, and chloride were normal, but the serum-bicarbonate was reduced to 20 mEq. per litre. Her total white-cell count was 12,700 per c.mm. (polymorphonuclears 62%), and the erythrocyte-sedimentation rate was 30 mm. in the 1st hour (Westergren).

At 8 P.M. she was given 50% glucose 40 ml. and hydrocortisone 100 mg. intravenously, without alteration in her level of consciousness. A stomach-tube was passed, and 20% glucose 150 ml. was given hourly. At midnight her blood-pressure had fallen to 90/70 and a solution of dextrose 45% and saline 0·25% was given intravenously. At 3 A.M. the blood-pressure was unchanged, and she responded to pain. But at 5.25 A.M. the systolic pressure had fallen to 70 mm. Hg and a solution of noradrenaline 4 mg. in normal saline 500 ml. was given in the drip. At 5.30 A.M. her blood-pressure had risen to 100/75, and at 5.45 A.M. (i.e., 20 minutes after starting the noradrenaline drip) she spoke her first rational words, saying she was comfortable, without pain, and not feeling cold. At 9 A.M. the blood-sugar was 222 mg. per 100 ml.

Noradrenaline had to be continued intravenously for 5 days to keep the blood-pressure in the normal range. She also had hydrocortisone 550 mg. in the first 22 hours, followed by cortisone 150,100, and 50 mg. daily in the 1st, 2nd, and 3rd weeks respectively. Penicillin was given for 12 days, and vitamin-B complex with ascorbic acid (' Parenterovite ') 4 ml. daily for a week. Subsequent blood-sugar and serum-electrolyte estimations were normal.

An electroencephalogram (E.E.G.) on June 18 showed symmetrical rhythmic activity of 5–7 cycles per sec. at a voltage of 30–40 μV, without blocking response to visual attention, suggesting generalised disturbance and slowing of cerebral activity. At lumbar puncture on June 16 the C.S.F. contained 4 lymphocytes per c.mm. and 40 mg. protein per 100 ml. The chest and skull were normal radiographically.

After the period of coma she was uncooperative, attempting to remove the intravenous drip and the nasoœsophageal tube, and she was incontinent most of the time. She was deluded, thinking the house physician was her husband and that the nurses were the students' wives. On June 27 (16 days after admission) she became violent, shouting and throwing food at other patients, and she was transferred to the Maudsley Hospital.

Course in Maudsley Hospital

The patient's mental state fluctuated unpredictably, her behaviour ranging from apathy (when a nurse had to help her to dress) to restlessness, with shouting and aggressive outbursts. Her talking ran parallel with her behaviour, and at times she persistently importuned the staff with various requests. Her mood likewise fluctuated: at first she was usually agitated, tearful, and sometimes suspicious, but later she was more often euphoric. Her memory was seriously at fault: orientation was always imperfect and sometimes grossly incorrect. She misidentified the staff as near relatives, and again thought one of the doctors was her husband. She was unable to concentrate on simple tasks for long, and easy calculations were performed either incorrectly or not at all.

Her mental disturbance created a considerable nursing problem, but from Aug. 8 (2 months after the coma) the fluctuations settled into a calmer, rather foolish, euphoric state. She recognised people correctly, and only made moderate mistakes in orientation. On Aug. 18 she discharged herself from hospital.

Between June 30 and Aug. 18, while the patient was taking cortisone, the blood-sugar did not fall below 88 mg. per 100 ml.; the protein-bound iodine ranged from 3·3 to 5·3 mg. per 100 ml. and the radioiodine-uptake neck/thigh ratio was 3 (both within normal range); the thyrotrophic hormone was 4·6 milli-units per 100 ml. (normal 10–20). The E.E.G. on July 4 still showed symmetrical generalised abnormality, with postcentral activity at 8 and at 6–7 cycles per sec., as well as at 2–4 cycles per sec., all of which now tended to block when the eyes were opened; but by Aug. 7 the alpha-rhythm was at 9 cycles per sec., with much less slow activity.

Follow-up

Since leaving hospital the patient has been seen regularly, and she has taken cortisone 25 mg. daily. At first she was still liable to mood changes and her concentration was impaired, but in September, 1958, her husband thought she was better than she had been since her last child was born. She was cheerful and alert, and her libido had returned to normal. No abnormality could be detected in her mental state, and she looked very well. By October, 1958, she was doing her housework and helping in her husband's shop, being able to calculate quickly and accurately.

Discussion

Mechanism of Hypopituitary Coma and Response to Treatment

Many metabolic factors may precipitate coma in patients with hypopituitarism (Caughey 1958), and our patient certainly had an intercurrent infection, hypoglycæmia, and hypotensive changes. But hypotension per se, as opposed to postural hypotension, is not mentioned as a cause of coma by Caughey nor by Sheehan and Summers (1952).

Sheehan and Summers wrote: " It is not easy to assess the value of treatment of hypopituitary coma, because if the patients are left without treatment some of them recover from the coma

spontaneously and some die. Thus the only indications of the efficacy of any particular treatment are the rapidity of the clinical response and the proportion of the patients treated in this way who do show a response."

We consider that this patient would have died if noradrenaline had not been given, and that the rise in the level of consciousness from coma to rational spontaneous speech within 20 minutes indicates that hypotension was an important contributory factor in this case. Finnerty et al. (1954) showed that a fall in mean blood-pressure of 29–80 mm. Hg can cause alterations in consciousness, although variation between individuals is wide.

The combined action of hypoglycæmia and hypotension was displayed in a group of schizophrenic patients who—Marley (1956) found—could not be rendered comatose with 400–500 units of soluble insulin but required in addition the hypotensive effect of hexamethonium and the upright posture early in the hypoglycæmic period.

Mechanism of Production of Psychosis

If coma was due to altered metabolism of the central nervous system associated with hypotension, hypoglycæmia, and hypocorticism, then the transient organic psychosis is likely to have resulted from damage, albeit reversible, from the same causes.

The functional and pathological changes due to hypotension and hypoglycæmia are very similar. After operations in which the blood-pressure was below 80 mm. Hg, Berg et al. (1957) showed that disturbances in the E.E.G. lasted a few days. Permanent and profound mental changes were described by Allison (1956) and Bedford (1957). Similarly, delayed recovery from the effects of hypoglycæmia is well known; the distribution of neuronal necrosis in fatal cases was shown to be similar to that of anoxic lesions (Lawrence et al. 1942). Experimentally Gellhorn et al. (1938) found that both the anoxic stimulus of 6·2% oxygen and that of hypoglycæmia of around 40 mg. per 100 ml. were required to produce Cheyne-Stokes respiration in dogs.

The relation between the adrenocortical and pituitary hormones and cerebral activity is complex. Depression and paranoid psychoses have been reported in patients with Addison's disease, cortisone or hydrocortisone producing the greatest restoration of mental capacities (Woodbury 1958). Mental torpor, depression, and delusions were often observed in proven cases of hypopituitarism (Sheehan and Summers 1949), and the loss of alpha-rhythm in the E.E.G. in such cases was noted by Hughes and Summers (1956). It seems unlikely in our case that the mental changes were due to excess cortisone, as disorientation is not characteristic of such psychoses, although organic psychosis with delusions and hallucinations due to excess cortisone was recorded by Glaser (1953). But our patient's eventual return to the wellbeing which existed 10 years previously may be attributable to continued treatment with cortisone.

The relative contribution of hypotension, hypoglycæmia, and endocrine disturbances in producing coma and psychosis in this case must remain conjectural.

Summary

A 46-year-old woman with hypopituitarism was precipitated into coma by an infection and failed to regain consciousness after the administration of glucose and hydrocortisone; but when the fall in her blood-pressure was reversed with noradrenaline intravenously she was able to speak rationally within 20 minutes.

After the coma she had an organic psychosis which lasted for 3 months. From this she recovered completely.

The patient was under the care of Sir Russell Brain and Sir Aubrey Lewis, and we wish to thank them for their encouragement and help with this paper.

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PROLONGED DRUG TREATMENT FOR PULMONARY TUBERCULOSIS

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FIVE years ago, Hoyle, Nicholson, and Dawson described the immediate results of treating 142 patients with antituberculous drugs for at least nine months. At that time only 63 of the 142 patients had been observed for more than a year after completing treatment, and so the eventual outcome of this form of therapy could not be assessed. We review here the progress of these patients over the eight years in which they have been treated and subsequently observed.

Present Investigation

The detailed analyses made for the original study were lost in a fire. It is probable that all the patients in that series have been included in the present one, as a systematic review of the records yielded 193 patients fulfilling the requirements for inclusion. This rather larger number is made up by those in our care (C. H. and H. N.), as well as those originally in the care of the late Dr. Andrew Morland who were supervised by one of us (H. N.).

All patients who received antituberculous drugs for at least nine months before June, 1955, are included. 171 of these patients have been observed for two years, and 134 for three years, after completing drug treatment. 75 of them were treated surgically and by other methods as well as with drugs; but for the other 118 patients, drug therapy was the only definitive treatment. The two groups were similar as regards

TABLE I—EXTENT OF DISEASE AND TREATMENT OF 193 CASES OF PULMONARY TUBERCULOSIS

Extent of disease*	Drugs only	Surgery	Total
I ..	23	16	39
II ..	57	42	99
III ..	38	17	55
Total ..	118	75	193
Cavitation ..	60	56	116

* This is classified according to Foster-Carter et al. (1952): class I, not more than one zone in one lung involved; class II, unilateral or bilateral disease involving two or three zones; class III, bilateral disease affecting four or more zones.

the presence of cavitation, but a rather higher proportion of patients treated with drugs alone had extensive disease (table I).

152 patients were receiving antituberculous drugs for the first time. 41 had had previous treatment for short periods, regarded as inadequate by present standards, and 35 of these were in the group of 118 patients treated by drugs alone.

Radiographic evidence of cavities was established and closure confirmed by tomography in almost all cases. Nodules were defined as uniformly dense foci over 1 cm. in diameter, in the plain film or tomograph, whichever was the greater. When bacterial resistance was measured the following standards were used:

	*Streptomycin**	*P.A.S.**	*Isoniazid**
Partially resistant	3	2	1·0
Resistant	10	10	5·0

* µg. per ml.

Progress was measured mainly by bacterial and radiographic methods. Sputum concentrates were examined monthly and cultures made until they repeatedly failed to grow *Mycobacterium tuberculosis*. Radiographic progress was followed with monthly posteroanterior films. The final results of treatment were judged by the ability of patients to resume and continue their normal lives. Relapse was recognised by radiographic extension of disease, by the appearance of cavitation, or by return of a positive sputum.

TABLE II—DURATION OF DRUG TREATMENT

—	No. of patients	Duration of treatment (mos.)			
		9–12	13–18	19–24	Over 24
Extent of disease:					
I	39	24	6	6	3
II	99	33	24	30	12
III	55	7	19	10	19
Total	193	64	49	46	34
Surgery and artificial pneumothorax ..	75	33	21	12	9

Methods of Treatment

Drug regimens varied from patient to patient and over the years of the study, but all patients were treated with combinations of two or three drugs accepted as effective. The doses used were: streptomycin sulphate 1 g. daily; combined dihydrostreptomycin 0·5 g. and streptomycin 0·5 g. daily; *p*-aminosalicylic acid (P.A.S.) 6 g. twice daily; and isoniazid 100 mg. twice daily. The duration of drug treatment increased over the years mainly because of the evolution of ideas upon prolonged therapy, but it was also influenced by the extent of the disease. Patients treated surgically received less drug treatment (table II).

With 1 exception all patients were admitted to hospital and rested in bed for the first three to six months; most of them spent about six months at a sanatorium afterwards. Those with cavities were usually nursed with the cavity dependent for the first few months. In addition to antibacterial treatment 60 patients were treated surgically and 15 by artificial pneumothorax. The indications for additional treatment varied; sometimes withholding this was considered unjustifiable when the results of drug therapy alone were still unknown, especially in dealing with thick-walled cavities which persisted after six months' drug treatment and bed rest: there is now little doubt that some of these cavities would have closed after longer treatment with chemotherapy alone (table III).

TABLE III—INTERVALS FROM START OF TREATMENT TO CAVITY CLOSURE

Time of closure (mos.)	Drug treatment alone	Drugs plus surgery and other measures
0– 6	30	34
7–12	15	15
13–36	4	4
Total	49*	53
Failure to close	11	3

* In 4 other patients cavity closure was achieved with drugs, but operation was performed subsequently.

Results

Sputum Conversion

Myco. tuberculosis was isolated from the sputum of 140 of the 193 patients. Only 1 patient has a persistently positive sputum after completing treatment, although in 5 others bacilli continued to appear in the sputum for a year; in these the sputum became negative within the next two years while the same drug regimen was continued. Of 118 patients treated with drugs alone, 79 had initially a positive sputum which became negative in all but 1.

Cavity Closure

116 of the 193 patients had cavities, which were closed by drugs alone in 53 instances; in the earlier years of the study many patients were treated surgically within a year after drug treatment was started, and for this reason the influence of drug therapy on cavity closure cannot be fully assessed. The intervals from the start of treatment to cavity closure are shown in table III.

In 30 out of 60 patients treated by drugs alone the cavities closed within six months, and in a further 19 after six months to three years. 11 patients in this group were left with persisting cavities, but in only 1 did the sputum remain positive; in 8 the sputum was negative within a year, and in the 2 others within three years.

14 patients of the whole series had persisting cavities at the time drugs were stopped. 9 of these are alive with

TABLE IV—DATA ON 23 PATIENTS WHO RELAPSED.

Case no.	Extent of disease	Previous drug treatment	Length of drug treatment	Interval since stopping treatment	Type of relapse*	Sputum	Sensitivity †	Outcome
1	II	—	9 days	Under treatment	Cavity	Pos.	Satis.	Resection, well
2	III	+	5 mos.	,, ,,	New cavity	Neg.	..	Resection, well
3	III	—	6 ,,	,, ,,	Cavity	Pos.	Res., s	Fistula, dead
4	III	—	7 ,,	,, ,,	New cavity	Neg.	..	A.P., well
5	II	—	9 ,,	36 mos.	Ext. cavity	Pos.	Satis.	Thoracoplasty, well
6	I	—	9 ,,	18 ,,	Extension	Neg.	..	Drugs, well
7	III	—	11 ,,	12 ,,	,,	,,	..	No treatment, well
8	II	—	12 ,,	18 ,,	Ext. cavity	Pos.	Satis.	Pulmonary embolism, dead
9	III	—	12 ,,	48 ,,	Empyema	,,	Satis.	No treatment, well
10	III	+	12 ,,	Under treatment	Extension	Neg.	..	Well at first, later died from respiratory infection
11	I	+	12 ,,	12 mos.	,,	,,	..	Drugs, well
12	II	—	12 ,,	24 ,,	,,	,,	..	No treatment, well
13	II	—	13 ,,	6 ,,	New cavity	Pos.	Satis.	A.P., well
14	III	+	17 ,,	18 ,,	Cavity	,,	..	Drugs, well
15	III	—	17 ,,	24 ,,	Extension	Neg.	..	Drugs, well
16	III	—	21 ,,	3 ,,	Cavity	,,	..	Thoracoplasty, well
17	II	—	21 ,,	12 ,,	Nodule enlarged	,,	..	Drugs, excision mucocœle
18	II	+	22 ,,	Under treatment	Extension	Pos.	Res., s	Drugs, well
19	II	—	24 ,,	3 mos.	Cavity	,,	Satis.	Drugs, well
20	III	+	24 ,,	24 ,,	Extension	,,	..	No treatment
21	III	—	30 ,,	12 ,,	Nil radiologically	,,	Satis.	No treatment, well
22	III	+	39 ,,	18 ,,	Extension	Neg.	..	No treatment, well
23	III	—	39 ,,	30 ,,	Cavity	,,	..	No treatment, well

* The site was new in case 1, and the original site in the remainder.
† Satis. indicates full sensitivity to streptomycin (s), P.A.S., and isoniazid.

open cavities and a negative sputum, but 6 had a positive sputum at the end of treatment or subsequently; 3 have died of tuberculosis and 1 of respiratory failure.

Nodules

Of the 193 patients 35 had nodules, which were resected in 12. The other 23 all progressed satisfactorily under treatment with drugs alone. In 5 the lesions disappeared rapidly, and in 12 they shrank gradually and formed a linear shadow; in 5 the nodules remained the same size, and in 1 the progress could not be assessed adequately. 16 of the 23 patients have been followed for over three years after completing antituberculous drug therapy, and in no instance did cavitation occur within the solid lesion: of the 12 patients treated by lung resection only 2 received this sort of therapy because of cavitation within the nodule.

Relapse

Of the 193 patients, 23 (12%) relapsed from the beginning of treatment up to four years after drugs were stopped. (6 of these patients relapsed while receiving chemotherapy, but 17 [8%] relapsed after drug treatment was completed.) Of 118 patients treated with drugs alone, 3 relapsed during treatment and 15 (13%) relapsed subsequently. Details of these patients are given in table IV.

Of the 23 patients who relapsed, 13 had advanced disease and 8 had disease of moderate severity (table IV). 15 of the 23 had received nine to fifteen months' drug treatment and relapse occurred up to four years after treatment was stopped. 8 patients relapsed who had had over eighteen months' continuous drug treatment. The interval between discontinuance of drug treatment and relapse ranged from three months to four years; in 6 patients the interval was over two years.

19 of the 23 patients who relapsed are now well, with their disease stabilised. 5 of them were treated surgically and 2 had an artificial pneumothorax. 6 received further chemotherapy for about two years, while the remaining 6 were not given any further treatment but have remained well. 1 other patient is at present receiving further chemotherapy. The remaining 3 patients of the 23 who relapsed have died—2 from non-tuberculous causes and 1 from advanced tuberculosis of many years' standing.

Deaths

11 patients died during the eight years of observation—5 from tuberculosis, 3 from respiratory failure, and 3 from unrelated causes.

Drug Toxicity

60 of the 193 patients complained of symptoms attributed to antituberculous drug (table V). Vestibular symptoms usually disappeared when streptomycin was discontinued. Other side-effects were controlled with appropriate treatment, and therapy was usually not curtailed.

Outcome in 134 Patients Followed for Three Years after Completion of Drug Treatment

123 of the 134 patients have survived. 6 have open cavities but are well with a negative sputum, 17 have relapsed at some time within the three years, and 6 have severe breathlessness with bronchitis and are respiratory cripples. 116 are well and have resumed work.

Return to Work

Of 174 cases where records are available, 106 patients had returned to work in a year or less, 61 in two years, and 7 after more than two years.

TABLE V—SIDE-EFFECTS OF DRUG TREATMENT

Drug	Side-effect	No. of cases
Streptomycin	Tinnitus	2
	Giddiness	14
	Deafness	2
	Drug rash and fever	17
P.A.S.	Drug rash and fever	10
	Goitre	1
	Severe nausea	12
Isoniazid	Burning feet	1
Uncertain	Angioneurotic œdema	1

Discussion

The aims of antituberculous drug therapy are to achieve maximum resolution and permanent healing of the disease. Clinically these may be measured by negative sputum-cultures, closure of cavities, the patient's capacity to lead a normal life and the absence of relapses.

In the present group of patients the outcome with regard to sputum conversion has been very satisfactory. Of the 79 cases treated by drugs alone in which the sputum was initially positive, all but 1 became negative, although in some cases the sputum ceased to be positive only after many months of drug treatment, and in 5 instances sputum conversion was achieved after more than a year of continuous chemotherapy.

For reasons already discussed, we are unable to assess the effectiveness of antituberculous drugs in closing cavities, but we should like to emphasise that cavity closure after six months' therapy occurred in about a third of those cases treated with drugs alone. Failure to achieve cavity closure at six months should not be regarded as failure of chemotherapy. Cavitation persisting with a negative sputum has not in our series proved to be a precursor of relapse, but numbers were small. However, Raleigh (1957) suggests that this may be so; 50% of his 123 patients with negative sputum and persisting cavities relapsed over a period of two and a half years, following an average of sixteen months' treatment. If cavities persist and surgery is excluded, it is probably wise to continue antituberculous drug treatment beyond two years. Persisting cavitation in association with a positive sputum proved as serious as expected, in that 4 out of 6 such patients died.

In this series there are 182 surviving patients, and 174 are leading normal lives: 6 have chronic bronchitis and various degrees of respiratory failure impairing their capacity for work. Of 134 patients followed for over three years after stopping chemotherapy, 122 have survived and been rendered non-infectious, but complacency is dispelled when the numbers of patients who have relapsed are considered. Unfavourable radiological change or positive sputum occurred in 23 of the 193 patients—about 12%. Of these 23 patients, 7 had had previous chemotherapy and 7 were longstanding cases of pulmonary tuberculosis and had received various other treatments in the past. Among these patients who relapsed, radiological extension of the disease with cavitation was seen most frequently; in fewer patients extension occurred without cavitation. Spread of the disease to a new site or the finding of a positive sputum in the absence of radiological change was rare. 8 patients relapsed after receiving chemotherapy for more than eighteen months. 1 patient was known to have taken the drugs irregularly. Another had pneumoconiosis complicated by tuberculosis, while a further patient was found to have a mucocœle of the bronchus but no definite evidence of tuberculosis. In the 4th patient cavity closure was believed to have occurred within three months of starting treatment; subsequently three months after treatment was stopped tomography demonstrated a cavity in the original situation, casting some doubt on the completeness of the first tomographs. The 5th patient had a persisting cavity under a thoracoplasty with a positive sputum. On routine tomography the 6th was found to have unsuspected rarefaction in a nodule approximately a centimeter in diameter; no further treatment was given, and a year later tomography disclosed a small stellate shadow at the site of rarefaction. 2 patients had had previous inadequate chemotherapy before their definitive course, and afterwards

developed slight extension of their disease. 1 patient is at present under treatment, but the other 7 have done well and are living normal lives with their disease apparently stabilised. In general the outcome in patients who relapsed is satisfactory in that 19 of 23 are well with their disease inactive.

Microbial persistence must be the ultimate reason for failure of chemotherapy (McDermott 1958). At a clinical level, several factors are important. Patients may fail to take the drugs prescribed, and this is now a well-recognised difficulty in long-term ambulant therapy. Gastrointestinal symptoms, so frequently produced by P.A.S., are particularly important in this respect. The importance of drug-resistant organisms has been stressed by Ross et al. (1958), but in our group drug resistance was infrequent. Usually it was found in those patients who had had previous inadequate chemotherapy. Previous treatment, however, may prejudice future chemotherapy in other ways as yet undetermined, encouraging microbial persistence without causing insusceptibility to drugs as shown by in-vitro methods (McDermott 1958). The length of time during which drugs should be given remains obscure. Ross et al. (1958) report a trend towards an inverse relationship between relapse and duration of treatment, but 63 of their patients treated for more than eighteen months had not relapsed at the time of their report, though the period of follow-up of these patients was only eighteen to thirty months. Smart and Gough (1958) reported no instances of relapse in a group of 75 patients who received chemotherapy for over a year; but the majority of their patients (45/75) were followed for less than two years after completing treatment. Relapse has, however, been observed in patients who have received two years' continuous drug therapy, both in the present and in other series (Raleigh 1957). This fact, together with the finding of drug-susceptible organisms in some of these cases, suggests that two years' treatment is sometimes insufficient. In our view all cases of active pulmonary tuberculosis, even when very slight, should receive at least two years' drug therapy.

Summary

The progress of 193 patients with pulmonary tuberculosis who received at least nine months' antibacterial drug treatment before June, 1955, has been reviewed.

The duration of treatment was over eighteen months in 80 patients; and 118 were treated with drugs alone. 134 were followed for more than three years after completing treatment.

At completion of treatment sputum culture for *Myco. tuberculosis* was negative in all patients except 1.

Of 60 patients with cavities who were treated by drugs alone, the cavities closed in less than six months in 30. In a further 19 the cavities closed after persisting for from six months to three years.

In each of 23 patients with nodules treated by drugs alone, the progress was satisfactory. 16 of these patients were followed for over three years after completing treatment.

12% of the whole group relapsed between the beginning of treatment and up to four years after drug treatment was discontinued. Of 118 patients treated with drugs alone, 13% relapsed after treatment was stopped.

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TRANSPOSITION OF THE VISCERA AND STERILITY IN MEN

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TRANSPOSITION of the viscera may be partial or complete. In 1947 Torgersen collected 129 cases, 123 of which were complete.

The reported frequency differs. In necropsy material it has been found to be 1 in 6000 and in a mass chest survey 1 in 6500 (Blegen 1949). Torgersen (1947) found that the frequency was 1 in 8000–10,000. Familial occurrence has been reported several times (Call and Woolf 1934, Cockayne 1937, Feldmann 1935, Feldmann and Needle 1934, Torgersen 1947 a and b). Torgersen reported consanguinity in 7·3% of the cases. Published accounts seem to indicate that cases may occur in the line of ascent and descent (Doolittle 1907, Torgersen 1947 a and b).

The ætiology is unknown. It has been suggested that the anomaly may be related to twins one of which has been absorbed in utero.

As regards external signs Ebstein (1923) reported that the right half of the scrotum hung further down than the left in 28 out of 36 men with complete transposition of the viscera. Left-handedness is not believed to be commoner in persons with visceral transposition than in others (Cockayne 1937).

The diagnosis may be made by percussion or auscultation, but should be confirmed by electrocardiography and by X-ray examination of the chest and gastrointestinal tract (Wood and Blalock 1940).

So-called Kartagener's syndrome is said to be common in these cases. It consists in visceral transposition, bronchiectasis, and malformation of the nasal sinuses (Cockayne 1937, Karani 1952). Torgersen (1947) found bronchiectasis in 8% of his cases.

No mention seems to have been made of sterility or reduced fertility in cases of visceral transposition.

Present Series

My series consists of 4 cases (3 male and 1 female) of complete visceral transposition among two sibships. Consanguinity in a high degree is present; the fathers are brothers and the mothers sisters, so the children are double first cousins. In addition, the parents have common greatgrandparents (fig. 1).

Of external signs which might indicate visceral transposition, in all 3 men the right half of the scrotum hangs lower than the left and 2 of them are left-handed. There are no other external peculiarities, and all the men are of masculine build.

All have a history of mild attacks of asthma; their colds have tended to be lengthy with much expectoration. 1 of the men has undergone an operation for frontal sinusitis, and another has diabetes mellitus. The woman has had an operation for acute appendicitis, and the appendix was found to be localised to the left side of the abdomen.

Electrocardiographic tracings showed in all cases total inversion of lead I and transposition of leads II and III (fig. 2).

Radiography in case D (see fig. 1) showed the liver in the left side of the abdomen, and total inversion of the stomach and colon was found after administration of contrast medium; chest radiography revealed complete transposition of the heart (figs. 3–5).

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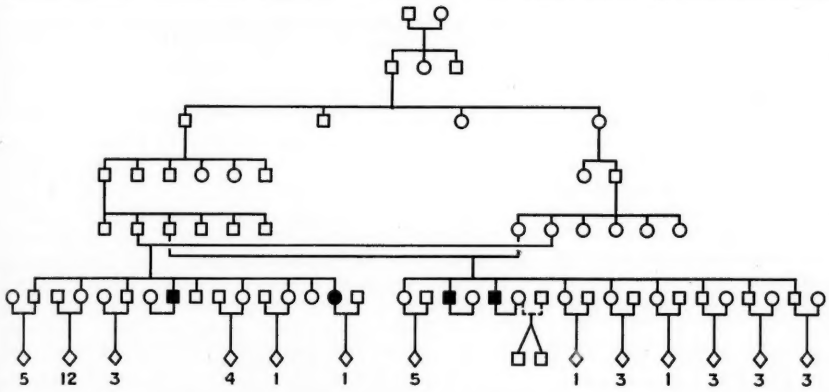

Fig. 1—Family tree showing two sibships of 9 members each. In one there is 1 man and 1 woman and in the other 2 men with complete transposition of the viscera.

Other members of the family, who were scattered all over the country, have been examined; nearly all were examined by electrocardiography and chest radiography and the remainder only by percussion and auscultation and, in males, inspection of the scrotum. No sign of visceral transposition was detected.

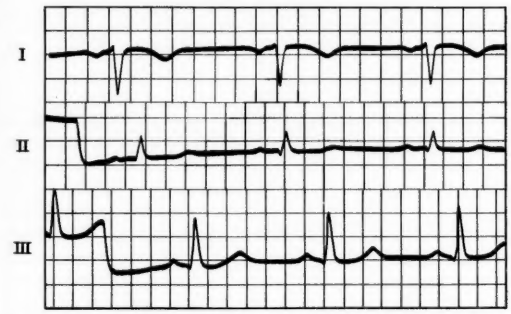

Fig. 2—Case D: electrocardiogram showing total inversion of lead I and transposition of leads II and III.

The family tree (fig. 1) shows 9 siblings in each sibship. All who are married have children except the men with visceral transposition, whereas the woman with visceral transposition has 1 child. Moreover, 1 of the men—case D—is married to a woman who has 2 sons born prior to the present marriage.

I tried to investigate the affected men as regards fertility. But 2 of them were over 50 years of age and so were their wives, and they refused to be examined. The 3rd man (case D), however, is married to a woman of child-bearing age, who had given birth to 2 sons before the present marriage, and they want children; so he declared himself willing to be examined.

Dr. Richard Hannen investigated case D's semen. The specimen consisted of 3·5 ml. of rather viscid, slightly transparent seminal fluid. Three-quarters of an hour after ejaculation 91% of spermatozoa were immobile; the survival-time was less than twenty-four hours after the ejaculation. Spermatozoa numbered 95,000,000 per ml. and the total number 333,000,000; 47% had abnormal head shapes. Dr. Hammen concluded that fertility was much reduced.

The genitalia appeared normal except for the right half of the scrotum hanging lower than the left; the testes were walnut-sized and firm.

A biopsy specimen of the right testis (examined by Dr. H. Olesen) contained particles of testicular tissue with numerous tubules; most of these were of normal width, but a few were somewhat narrow with mild fibrous thickening of the tubular walls. Throughout, they were lined with very tall columnar epithelium, containing all elements and with very brisk spermiogenesis; but some spermatozoa were thin with somewhat pear-shaped heads. There were no clear degenerative changes of the epithelial tissue. The interstitial tissue was sparse, with very small groups of Leydig cells; no inflammatory reaction. Dr. H. Olesen concluded that the testicular tissue showed slight degenerative changes and brisk, somewhat abnormal spermiogenesis.

Basal metabolic rate +11% (determined twice). Hormone analyses: Gonadotrophins below 50 milli-units; total and fractionated 17-ketosteroids normal.

The cases in this family suggest that men with transposition of the viscera may be infertile or subfertile. This point should be further investigated in other patients with the condition, and, if confirmed, a watch should be kept for transposition of the viscera among patients at male sterility clinics.

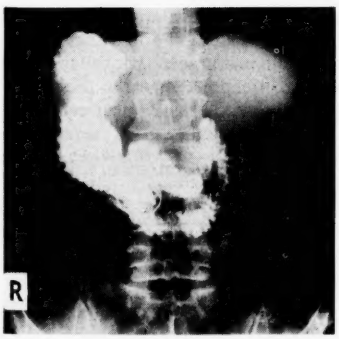

Fig. 3—Case D: X-ray film after barium meal showing stomach on the right side.

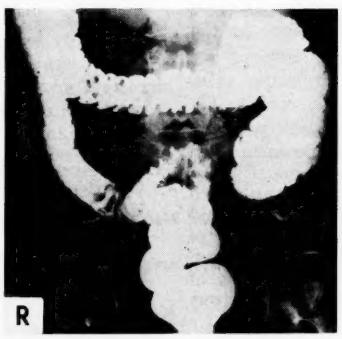

Fig. 4—Case D: X-ray film of colon after barium enema showing ascending colon on left and descending colon on right.

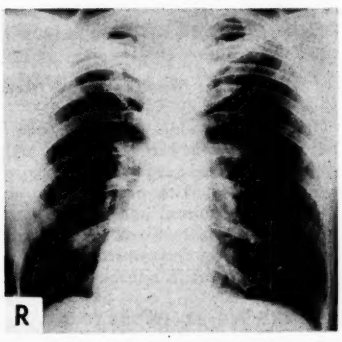

Fig. 5—Case D: chest radiograph showing transposition of heart.

Summary

Two sibships, each of 9 members, includes 4 cases of transposition of the viscera (3 men and 1 woman).

There is a high degree of consanguinity, as their mothers are sisters and their fathers brothers, and the parents have common greatgrandparents. All except 1 woman and 1 man are married, and all those who are married have had children except the men with visceral transposition. 1 of these, married to a woman who had borne 2 sons before the present marriage, was investigated more closely; examination of seminal fluid and biopsy of the testis suggested reduced fertility.

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PRODUCTION OF VIRÆMIA IN CORTISONE-TREATED MONKEYS WITH THE ATTENUATED BRUNENDERS STRAIN OF TYPE-1 POLIOVIRUS

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MUCH of the information on the infectivity for monkeys of the strains of poliovirus used for the production of formalin-inactivated vaccines has been obtained from investigations with virulent strains (Bodian 1956, Eklund et al. 1956, Gebhardt and Bachtold 1956, Syverton et al. 1956). In Britain, however, the attenuated Brunenders strain of poliomyelitis virus is used as the type-1 component of poliomyelitis vaccine (Biological Standards Control Laboratory 1957) and information on the infectivity of this strain for monkeys was required so that satisfactory procedures could be adopted for testing vaccines manufactured in this country. A series of experiments was carried out, therefore, in which cortisone-treated cynomolgus monkeys were injected with varying doses of the Brunenders strain. These experiments provided information on the occurrence of viræmia and on the ability of the strain to produce lesions in the central nervous system.

Materials and Methods

Animals

Cynomolgus monkeys (*Macaca irus philippinensis*) weighing between 1·4 and 1·8 kg. were used. They were in good condition and had been in quarantine for at least a month before use. Before injection of virus each animal was anæsthetised by an intraperitoneal injection of pentobarbitone sodium and also given 300,000 units of long-acting penicillin and 0·4 g. of chloramphenicol intramuscularly. All monkeys were given 150 mg. cortisone intramuscularly 2 days before injection of virus, and 100, 50, 75, 50, 50, 75, 50, and 50 mg. respectively at 0, 2, 4, 7, 9, 11, 14, and 16 days thereafter.

Inoculation of Virus

Suspensions of living virus were prepared in either commercial poliomyelitis vaccine or medium 199 (Morgan, Morton, and Parker 1950) as described previously (Coid, Beswick, and Tobin 1960). The total dose of virus given to each monkey varied between 3 and 140 $TCID_{50}$ and was contained in a volume of 3·4 ml., each animal receiving 0·3 ml. into each thalamus, 0·1 ml. into each of three lumbar segments, and 2·5 ml. into the right deltoid muscle.

Isolation of Virus from Blood-serum

Blood samples were taken from the femoral vein at intervals between the 3rd and 18th day after injection and from the heart at the time of death. Virus was isolated from the serum using monkey-kidney cell cultures by the method previously described, and all isolates were typed to confirm that they were type-1 poliovirus (Coid, Beswick, and Tobin 1960).

Histological Examination

At the end of the observation period, which varied from 21 to 25 days, or at the time when paralysis developed, the animals were anæsthetised with pentobarbitone sodium and perfused with formol-saline, and the brains and spinal cords were removed for histological examination (Biological Standards Control Laboratory 1957).

TABLE I—TIME AFTER INJECTION WHEN VIRUS WAS FIRST ISOLATED FROM THE SERA OF MONKEYS INJECTED WITH TYPE-1 POLIOMYELITIS VIRUS

Virus suspended in	No. of serum samples in which virus was first isolated (days after injection)				Total
	3	7	10–11	15–18	
Poliomyelitis vaccine	4	2	2	4	12
Medium 199 ..	1	7	3	2	13
Total ..	5	9	5	6	25

Results

A total of sixty-eight monkeys were injected over a period of approximately 18 months, forty-one receiving virus suspended in poliomyelitis vaccine and twenty-seven virus suspended in medium 199. Viræmia was detected in twenty-five monkeys—in twelve of those receiving virus in vaccine and thirteen of those receiving virus in medium 199. In sixteen of the twenty-five monkeys virus was isolated on one occasion only and in the remaining nine at least twice from consecutive blood samples. The results, giving the time at which virus was first isolated from the blood, are shown in table I. It is evident that the first isolations did not occur at any particular time after injection and that there is no obvious difference in the results obtained with virus in vaccine and virus in medium 199. It is interesting to note that 6 of the first isolations occurred as late as between 15 and 18 days after the injection of virus; and of these 2 were isolated actually on the 18th day. The levels of virus found in monkeys injected with the highest dose of virus varied from minimal amounts to 10^4 $TCID_{50}$ per ml.

In table II these results are compared with those obtained by histological examination. When the results of both tests are taken together it is seen that thirty-three monkeys gave evidence of infection; in eight there was histological evidence only, in twelve serological evidence, only and in thirteen both histological and serological

TABLE II—COMPARISON OF VIRÆMIA WITH HISTOLOGICAL EVIDENCE OF INFECTION IN MONKEYS INJECTED WITH TYPE-1 POLIOMYELITIS VIRUS

Virus suspended in	No. of animals with			Total no. of animals infected
	C.N.S. lesions only	Viræmia only	Viræmia and C.N.S. lesions	
Poliomyelitis vaccine	5	7	5	17
Medium 199 ..	3	5	8	16
Total ..	8	12	13	33

evidence. Therefore, if histological examination alone had been made infection would have been detected in only twenty-one monkeys, and if serological examination alone had been made only twenty-five would have shown infection. Again, there was no obvious difference in the results obtained with virus in vaccine and virus in medium 199.

Conclusions

In the safety testing of inactivated poliomyelitis vaccine in monkeys it is important that the procedures adopted should ensure that no chance of detecting the presence of live virus is missed. The experiments described, using the attenuated Brunenders type-1 strain, have shown that combining the histological examination of the central nervous system with the examination of the blood for the presence of virus is more satisfactory in detecting infection than either method alone.

It is evident also that if infections are not to be missed the examination of blood samples must be made at regular intervals during the observation period and at least up to the 18th day.

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VITAMIN-A DEFICIENCY FOLLOWING TOTAL GASTRECTOMY

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THE operation of total gastrectomy is relatively rare and is often followed by digestive and other complications.

The sequelæ of the operation have been much investigated; but we have been unable to find any record of vitamin-A deficiency, with dermatological lesions or impaired night vision, developing after this operation. In the course of a long-term study of the metabolic effects of total gastrectomy the five patients described in this paper were all found to be deficient in vitamin A.

Material and Methods

Total gastrectomy, with œsophagojejunal anastomosis, was performed for histologically proven carcinoma in cases 1, 3, and 5 and for gastric stenosis due to corrosive gastritis in case 4; a tiny fringe of fundus was left to facilitate the anastomosis after the removal of a clinically malignant, but histologically benign, gastric ulcer in case 2, who also underwent partial pancreatectomy and who later developed diabetes mellitus. At the time of this study there was no evidence of recurrent carcinoma in cases 1, 3, and 5.

Serum-vitamin-A concentrations were estimated by the method of Kaser and Stekol (1943).

Vitamin-A-absorption tests were carried out in four cases after an 8-hour fast. A fasting blood sample and further samples at 2, 4, and 6 hours after approximately 200,000 I.U. vitamin-A palmitate in olive oil (7 ml. 'Avoleum', B.D.H.) orally were collected, no food being permitted during the test. The absorption tests were repeated after treatment with oral vitamin A 100,000 I.U. daily for 2–3 weeks.

Dark-adapted visual acuity was assessed before and 2–3 weeks after treatment with oral vitamin A, by the method of Riddell (1940, 1943), the examiner being unaware of any treatment given, or of the biochemical findings.

Jejunal biopsies were obtained, without overt bleeding, using a biopsy tube (Wood et al. 1949) passed under radiological control. Specimens were fixed immediately in 10% formol-saline followed by formol-corrosive, and paraffin sections were stained by hæmalum and eosin, trichrome stains, mucicarmine (Southgate), van Gieson, diazo (Pearce), reticulin (Gordon and Sweet), and periodic-acid Schiff reagent.

Fat absorption was assessed over a 4-day (case 3) or 10-day balance period, the daily intake of fat being 50 g.

A detailed dietary history was obtained by standard methods, particular reference being paid to the carotene and preformed vitamin-A content of the diet.

TABLE II—RESULTS OF VITAMIN-A-ABSORPTION TESTS

Case no.	Relation to treatment	Serum-vitamin-A levels (μg. per 100 ml.)			
		0 hr.	2 hr.	4 hr.	6 hr.
1	Before	9	—	40	—
	After	30	20	155	65
2	Before	13	—	95	—
	After	33	258	370	358
4	Before	8	—	40	—
	After	40	35	165	90
5	Before	12	—	50	—
	After	46	248	190	89

Results

Vitamin A.—The results of the biochemical studies are given in tables I and II. The initial value (table I) refers to the vitamin-A concentration of serum obtained from the patients when they first came under observation and stored at −20°C until analysed. In four cases vitamin-A absorption tests (table II) were carried out and the estimations were made immediately. The fasting values were subnormal in all cases, and, although there was evidence of absorption shown by a rise in the serum-vitamin-A concentration, the peak values were less than those obtained in normal subjects. When the tests were repeated after oral treatment with vitamin A the fasting concentrations and peak values were then normal.

Dark-adapted vision.—Before treatment dark-adapted vision was subnormal in four cases (table I), three of whom were retested after vitamin-A therapy and all had returned to normal. In the fifth case dark-adapted vision

TABLE I—DATA ON 5 CASES OF VITAMIN-A DEFICIENCY FOLLOWING GASTRECTOMY

Case no.	Age (yr.)	Sex	Time since operation (yr.)	Fat absorption (%)	Daily vitamin-A intake (I.U.)	Initial serum-vitamin-A level (μg per 100 ml.)	Skin lesions	Dark-adapted visual acuity	
								Before treatment	After treatment
1	48	F	5¾	54	4368	4	..	Subnormal	Normal
2	42	M	5	79	5360	9	..	„	„
3	47	M	2	90	3178	4	..	„	Not tested
4	60	M	13	88	5590	3	+	Normal	Normal
5	47	M	1⅓	76	6413	10	..	Subnormal	„

was normal: this patient had follicular hyperkeratosis of the type described in vitamin-A deficiency.

Fat absorption.—The amount of dietary fat absorbed was much impaired in three cases, and in the other two was just below the usually accepted lower limit of normality (table I).

Jejunal biopsies.—In all instances the appearances of the jejunal mucosa obtained was considered to be within normal limits although minor variations were occasionally noted, such as slight widening of the villi (case 1) and slight reduction in total mucosal thickness (case 4).

Diet.—In all cases the intake of vitamin A was within normal limits. The bulk of the total vitamin A ingested was in the form of the preformed vitamin. The intake of vitamin A in table I refers to preformed vitamin A only.

Discussion

There is good evidence that all of these patients were suffering from vitamin-A deficiency. All had very low serum-vitamin-A concentrations, and these were raised to normal in the four cases given oral vitamin A; the defective dark adaptation demonstrated in four patients was corrected by oral vitamin A in the three patients who were retested; the one patient who had normal dark adaptation had follicular hyperkeratosis which was cured by oral vitamin A. None of the night-blind patients were aware of the defect, but this was not unexpected as all were city-dwellers. Follicular hyperkeratosis due to vitamin-A deficiency is extremely rare in this country (Bicknell and Prescott 1953).

The ideal intake of vitamin A is not known with certainty, but a daily intake of 2500 I.U. is considered satisfactory (Medical Research Council 1949), and we accept that all these patients had an adequate intake well within normal limits. No patient took liquid paraffin, which hinders the absorption of vitamin A, and no patient had any intercurrent disease in which vitamin-A deficiency is known to occur as a complication, diabetes mellitus no longer being considered to be a cause of perverted vitamin-A metabolism (Bicknell and Prescott 1953, Moore 1957). Under these circumstances, and because the operation was performed for different lesions, it is difficult to escape the conclusion that the deficiency is, in some way, the result of the operation. One patient, not included in this series, had a normal serum-vitamin-A concentration prior to total gastrectomy and one year after operation; this suggests that the deficiency is a late result of operation possibly due to depletion of body reserves and not an immediate metabolic consequence such as might happen in pneumonia.

The cause of the deficiency is an interesting problem. From what is known of the biochemistry of fat and vitamin-A absorption it is reasonable to suppose that the absorption of vitamin A would be reduced in direct proportion to the degree of fat malabsorption. When fat absorption is normal or only slightly impaired, and when the dietary intake of vitamin A is high, as in cases 2 and 4 in particular, it is unreasonable to ascribe the vitamin-A deficiency solely to steatorrhœa. Of the cases reported here, there is only one (case 1) in which steatorrhœa alone might possibly have caused the vitamin deficiency.

The view that steatorrhœa per se is a cause of vitamin-A deficiency is based largely on study of patients with gluten-induced enteropathy, many of whom fail to absorb vitamin A as judged by the test used here; but in such patients there is an anatomical abnormality of the small bowel which may be the cause of the malabsorption of both fat and vitamin A. In our cases there was no evidence of any lesion comparable to that seen in gluten-induced enteropathy and sometimes seen in other types of steatorrhœa (Paulley 1954, Doniach and Shiner 1957, Sakula and Shiner 1957, Shiner 1957, 1959, Butterworth and Perez-Santiago 1958). In two cases only (cases 1 and 4) there were minor histological variations which we do not regard as differing significantly from normal; similar changes were seen in control biopsy material and were obviously the result of processing. This is in keeping with the general experience of those who have studied the jejunum microscopically after subtotal gastrectomy. Baird and Dodge (1957) found that the jejunal mucosa was normal in twenty-three out of thirty-one patients after partial gastrectomy, the remaining eight cases showing minor variations only. After partial gastrectomy Doniach and Shiner (1957) found abnormalities in the jejunal mucosa of one of their four cases, while in a series of fifteen patients with post-gastrectomy steatorrhœa described by Shiner (1959) jejunal villous atrophy, partial or subtotal, was observed in only two cases. Paulley (1959) attaches more significance to minor variations than do others. It is to be noted that three of our samples (cases 1, 2, and 4) were obtained after the patients had been treated for post-gastrectomy megaloblastic anæmia; and since it is known that atrophic villi may regenerate after therapy in cases of steatorrhœa, other than the gluten-induced variety, it is perhaps possible that significant changes might have been found had the samples been taken before therapy; the clinical condition of the patients did not permit this.

The limitations of the absorption test as a means of estimating the degree of absorption of ingested vitamin A in the same individual, as well as between individuals, are well known (Hillman and Becker 1957, Volwiler 1957), but it does appear that our patients can absorb at least some of the large dose of vitamin A used in the test. The low peak values obtained in the initial tests, while the patients were in a grossly deficient state, may represent rapid clearance of the absorbed vitamin to body tissues—a feature not evident when the tests were repeated after a period of treatment when the body stores would have been replenished.

The cause of the deficiency in these patients with normal dietary intakes, normal histological appearances of the small bowel, and apparently normal absorption of massive doses of vitamin A is obscure, but may well lie in a multiplicity of factors resulting from the operation which act to the detriment of the absorption of physiological amounts of vitamin A but do not apparently hinder absorption of massive amounts, as far as can be judged by the test used.

Relatively little is known with certainty about the site of absorption and the factors governing the absorption of vitamin A in man even when the gastrointestinal tract is intact. There is good evidence that the site of maximal absorption in rats and ruminants is in the upper small bowel (Popper and Volk 1944, Eden and Sellers 1949) and there is some evidence that this may be so in man (Fingerland 1957). What is known of the factors governing absorption is based largely on the results of absorption tests of the type used here and is therefore liable to misinterpretation.

An adequate intake of fat in the diet and the presence of lipolytic enzymes in bile appear to be necessary for the normal absorption of vitamin A, while decreased intestinal motility apparently impairs absorption (Bicknell and Prescott 1953, Moore 1957). All our patients had a normal fat intake. The most obvious abnormality in our patients is

the loss of the reservoir and digestive function of the stomach with consequent premature passage of a large mass of inadequately digested food relatively low down in the small bowel and rapid transit through the small bowel past the absorbing sites. We have been impressed by the very rapid transit of a barium bolus in our patients.

Other factors which may also be important are the limited time available for mixing of the bolus with, and digestion by, pancreatic enzymes before the mass reaches the absorbing site, the limited amount of pancreatic enzymes and bile which will be available particularly where the anastomosis is œsophagojejunal rather than œsophagoduodenal (notably where partial pancreatectomy has also been performed as in case 2), and finally the unknown quantity of abnormal bacterial proliferation in the small bowel. Until an absorption test using physiological quantities of vitamin A is devised, it is unlikely that the precise cause of the deficiency will be found.

The deficiency of vitamin A in our patients does not seem to be a very severe matter in itself, and it does not seem to be comparable to the gross degrees which cause keratomalacia. Nevertheless we cannot regard the deficiency as other than detrimental to good health, and it would seem desirable to give vitamin A to patients after total gastrectomy as a prophylactic measure. On the basis of the present investigations, which are continuing, a course of oral vitamin A, 100,000 I.U. daily for 2 weeks every six months, seems advisable. On this regime there is no risk of the toxic effects which might result from large daily doses for long periods.

Summary

Five cases of vitamin-A deficiency in patients who had undergone total gastrectomy are reported. Four of the patients were night-blind and the fifth had follicular hyperkeratosis. These abnormalities were corrected in the four cases given oral vitamin A.

The deficiency is of complex origin, and steatorrhœa is not the only causal factor.

Vitamin A should be administered prophylactically to patients who have undergone gastrectomy.

We are grateful to Dr. J. A. W. McCluskie, Prof. D. F. Cappell, Prof. W. J. B. Riddell, and Dr. E. B. Hendry for advice and criticism, and to Dr. A. C. Macdonald and Dr. D. Horne for facilities at the Vale of Leven Hospital; to Mr. Arthur Ness, of the department of biochemistry, Western Infirmary, Glasgow, for the serum-vitamin-A estimations, and to Miss M. G. McCombie, of the dietetic department, for the dietary histories; and to the physicians and surgeons of the Western Infirmary who have allowed us to study their patients.

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Preliminary Communication

THE REJECTION OF RENAL HOMOGRAFTS INHIBITION IN DOGS BY 6-MERCAPTOPURINE

FOLLOWING the report by Schwartz and Dameshek [1] that 6-mercaptopurine can make rabbits tolerant to human serum albumin antigen, I have used this drug in an attempt to modify the rejection of renal homografts in dogs.

1. Schwartz, R., Dameshek, W. *Nature, Lond.* 1959, **183,** 1682.

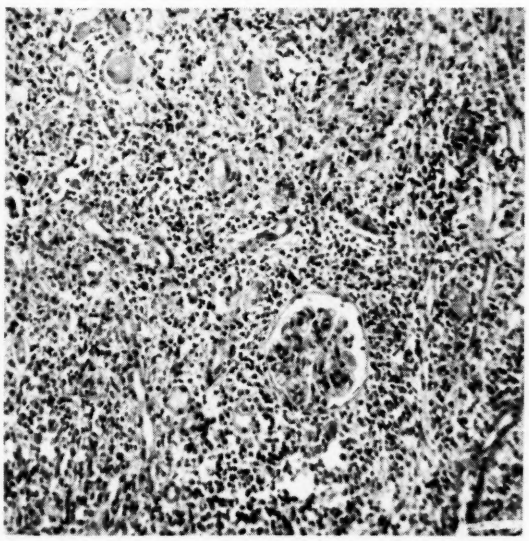

Fig. 1—Typical homograft reaction with intense cellular infiltration in a kidney 10 days after transplantation. (Hæmotoxylin and eosin. ×120.)

INVESTIGATION

The donor and recipient dogs were of different breeds. Under intravenous pentobarbitone anæsthesia, a kidney was removed from the donor and transplanted to the right iliac fossa of the recipient; the renal vessels of the donor's kidney were anastomosed to the iliac vessels of the recipient and the ureter was implanted into the bladder.

Given by intramuscular injection, in a dosage of 6 mg. per kg. body-weight daily from the operation, 6-mercaptopurine proved highly toxic. On the other hand, though the animals died from its effects in 10–14 days, they showed no signs of the homograft reaction described by Dempster [2] and Simonsen et al.[3] (fig. 1). On a lower but still toxic dosage in a dog

2. Dempster, W. J. *Brit. J. Surg.* 1953, **40,** 447.
3. Simonsen, M., Buemann, J., Gammeltoft, A., Jensen, F., Jorgensen, K. *Acta path. microbiol. scand.* 1953, **32,** 1.

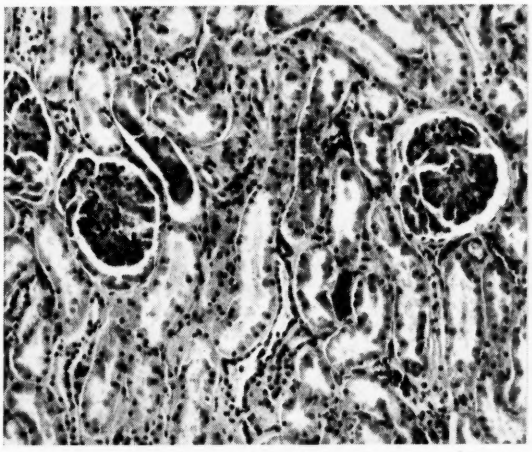

Fig. 2—Renal homotransplant after 47 days on 6-mercaptopurine. No evidence of homograft reaction. (H. & E. ×120.)

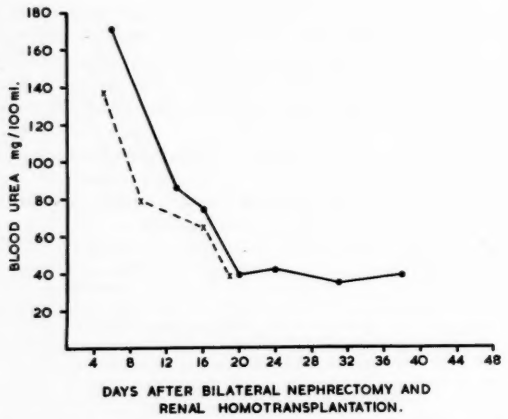

Fig. 3—Blood-urea levels in dogs surviving 21 and 47 days after bilateral nephrectomy and renal homotransplantation.

which had been off 6-mercaptopurine for six days owing to leucopæmia there was evidence at 12 days of cortical cellular infiltration, which was regarded as a mild homograft reaction.

In a second series of experiments, in order to assess the function of the transplanted kidney, bilateral nephrectomy was performed at the same time as the renal homotransplantation. The dosage of 6-mercaptopurine was 5 mg. per kg. intramuscularly for the first 2 days, 2·5 mg. per kg. intramuscularly for the next 4 days, and then 2·5 mg. per kg. daily by mouth except when the total white-cell count fell below 5000 per c.mm.

Several dogs on this regime died with oliguria 4–6 days after operation. No homograft reaction was found in the kidneys. Their death was thought to be due to a vicious circle of primary anuria, uræmia, and vomiting, leading to prerenal uræmia.

The two dogs surviving this critical period died of pneumonia, on the 21st and 47th days after operation. In the longer survivor the liver was bile-stained and showed intralobular biliary stasis; its parenchyma was not necrotic. In both dogs the grafted kidney was normal macroscopically, and microscopy revealed no evidence of the homograft reaction (fig. 2), although there were areas of hæmorrhage in the kidney that functioned for 21 days. Both animals were passing concentrated urine up to the time of death. The blood-urea levels are shown in fig. 3.

In an attempt to prevent the early deaths, the procedure was further modified by performing only unilateral nephrectomy at the time of renal transplantation, leaving removal of the second kidney till a later date.

DISCUSSION

In dogs first-stage renal homografts usually cease to function after 4–8 days, showing massive cellular infiltration. The longest periods of function in four recent series are 11 days,[2] 12 days,[3] 14 days,[4] and 20 days.[5] In an irradiated dog a renal homograft has survived 49 days,[6] and the kidney was found to be normal microscopically.

My observations with 6-mercaptopurine suggest that this drug can modify the rejection of renal homografts in dogs. It could have advantages over total body irradiation in being less hazardous, and possibly less crippling immunologically, though it seems to increase liability to infection and can cause hepatic biliary stasis.[7] Its use might thus offer an approach to renal homografting in man, especially in chronic uræmic patients in whom homograft rejection is already depressed.[8]

The effects observed could be explained either by a non-specific cytotoxic action of the drug on the immune system, or by a true specific production of immune tolerance. This problem is being investigated.

I am much indebted to Prof. D. Slome for his help and encouragement and to the council of the Royal College of Surgeons for providing facilities, materials and technical assistance at the Buckston Browne Research Farm, where this work was done. I am also grateful to Mr. J. P. Hopewell and Dr. K. A. Porter for their guidance and advice.

Burroughs Wellcome & Co. provided the 6-mercaptopurine, which was prepared for me in the dispensary of the Royal Free Hospital. The histological sections were made in the hospital's department of pathology.

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New Inventions

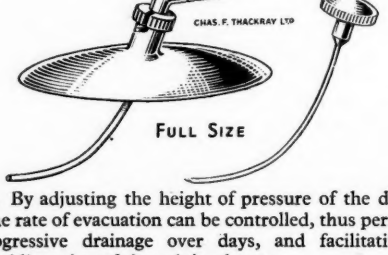
CANNULA FOR TREATMENT OF SUBDURAL EFFUSIONS IN INFANTS BY CONTINUOUS DRAINAGE

SUBDURAL effusion is fairly common in infancy and causes a high morbidity if neglected. Early treatment must be undertaken to avoid restriction of brain expansion and to prevent impairment of mental development. It is important, therefore, to remove the fluid which collects in the subdural space.

When the effusion is a true hæmatoma one or two subdural taps usually suffice. But if the effusion is a subdural hygroma, after subdural tap the fluid rapidly collects again from the subarachnoid space, being pumped up by leakage. Hence continuous drainage may be necessary to allow adhesive obliteration of the subdural space.

The immediate evacuation of large subdural effusions in infants carries a high mortality: an early, but gradual, release of pressure is preferable. The practice in some clinics is to perform subdural taps daily on alternate sides, removing 10–15 ml. of fluid each time. If the fontanelle quickly becomes tight again, or, if the baby's general condition is poor, it may be necessary to tap more frequently. For many years Prof. Norman Dott of Edinburgh has advocated a system of continuous drainage of the subdural space.

Continuous drainage avoids the need for multiple punctures —which can lead to infection—and reduces the distress caused to the child and the possibility of bleeding after frequent



needling. By adjusting the height of pressure of the drainage system the rate of evacuation can be controlled, thus permitting slow progressive drainage over days, and facilitating the adhesive obliteration of the subdural space.

With this method of treatment, operative excision of hæmatoma membrane will rarely be needed. (Such membrane, composed of fibrin, may form on the undersurface of the dura and become a " space-occupying lesion.")

The requirements of a continuous drainage cannula are:

1. It should be of reasonable calibre to permit free drainage without blockage.
2. With its attendant fine trochar it should easily enter the subdural space with a clean puncture and negligible trauma.

3. It should fit snugly and firmly to the scalp with the minimum of dressings. Unless it is secure, its movement may cause further bleeding in the subdural space.

4. The connection from the cannula to the drainage tube leading to the collecting-flask must be securely locked; loose attachments which are liable to come adrift lead to unsterile attempts at reconnection, with the possibility of infection.

The present cannula meets these criteria. The trochar and cannula are made of stainless steel and are size 18 or 19 B.W.G. The cannula is attached to the scalp shield at an angle of 30°. This allows it to drain the subdural space while the shield is firmly applied to the scalp. The fixity of the shield minimises movement of the cannula, which cannot " wiggle " or " move " inside the skull. The connecting link to the cannula is a ' Record ' pin locking movement which affords a firm connection and from which the rubber drainage tube leads to a conical half-pint collecting-flask. This flask is held in place at the end of the cot with a double clamp which can be raised or lowered, thus altering the head of pressure and enabling the rate of escape of the effusion to be controlled.

Procedure

The standard procedure for subdural tap in infancy is followed. The crown of the infant's head is carefully shaved and cleansed and held firmly in a sterile towel by an assistant. Professor Dott tells me that he has found the following cleansing technique satisfactory for preventing the infection which may arise with indwelling drainage tubes in the subdural space:

" The scalp is washed carefully with cetrimide (' Cetavlon ') and rinsed with saline. While it is still moist ' Polybactrin ' antibiotic spray is applied to the scalp. A blob of ' Cicatrin ' (antibiotic cream) is applied to the scalp on the site where the cannula puncture is to be made. In addition to its valuable antibiotic content the lubrication effect of the cicatrin cream makes for a clean and easy puncture."

A thin gauze dressing 2 or 3 mm. larger in diameter than the scalp shield is pierced centrally by the trochar and cannula and slid into position on the under-surface of the shield. The subdural space is then punctured and the trochar is immediately eased back; but it is not withdrawn, lest there should be a sudden uncontrolled release of the subdural effusion. The cannula is then gradually and gently slid into the subdural space, with the shield resting gently and evenly on the scalp. The trochar is withdrawn and the connecting-piece is locked in position, having already been connected by the rubber tube to the collecting-flask. The patency of the drainage having been established, the cannula is firmly fixed in position by placing four pieces of $^1/_2$-in. ' Sleek ' adhesive a few inches in length across the shield, crosswise, after cleansing the scalp with ether. In practice, even if the infant is restless, the cannula is very unlikely to work loose or disconnect, and routine nursing and feeding can be followed without hindrance.

The cannula should not be left in any one puncture site longer than three days. A few fresh punctures can of course be made, the complete drainage apparatus having been resterilised before reconnection, but the duration of continuous external drainage should be limited to two or three weeks at most. For the very occasional case where fluid is still collecting after three weeks, the extra-light-opening-type of Spitz-Holtzer valve might perhaps be used as a means of closed internal drainage.

I am grateful to Prof. Norman Dott and to Mr. W. R. Henderson; and also to Mr. Lockhart, of Messrs. Charles F. Thackray & Sons, Leeds, who manufactured the cannula.

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Reviews of Books

Human Biochemical Genetics

H. HARRIS, M.D., reader in biochemical genetics, London Hospital Medical College. London: Cambridge University Press. 1959. Pp. 310. 37*s*. 6*d*.

DURING the past three years there has been a flush of books, articles, and symposia on various aspects of human biochemical genetics. This is no more than it should be. " From being an obscure subject, supposedly only pursued by academically minded cranks and of little significance in therapeutics, the study of inborn metabolic errors is becoming a very important branch of medicine ": so wrote Penrose in 1957. This excellent book, written by one of the leaders in the field, has come at an opportune moment. The literature has been scattered among the biochemical, medical, and genetical journals, so that many doctors have been slow to grasp the enormous impact of this subject on clinical medicine. Already, however, many of the larger medical schools, in the admittedly specialist-minded United States, are pondering the establishment of departments of medical genetics.

The book begins with an introductory account of the principles of human population genetics. Disturbances of aminoacid metabolism, carbohydrate metabolism, human hæmoglobins, blood-group substances, and plasma-proteins are among the subjects discussed informatively. They are, moreover, discussed not from the viewpont, too often adopted these days, of metabolic defects which " happen to be inherited " but from the more sophisticated viewpoint of problems in classical biochemical genetics. Inevitably the book reflects the author's interests and experience and would not claim to be encyclopædic.

The chapter on the human hæmoglobins is as up to date as possible in a rapidly moving subject. Dr. Harris properly lays emphasis on the extraordinary fact that the substitution of a single aminoacid (valine for glutamic acid, for example) in a hæmoglobin molecule consisting of approximately 560 aminoacids can result in the difference between normal and sickle-cell hæmoglobin—between health and disease. Unquestionably, many aspects of this section will need to be rewritten and enlarged in future editions. The aminoacid sequence in the anomalous peptides of hæmoglobin C and S (illustrated in fig. 46) will have to be revised in the light of Ingram's recent work. The details are less important, however, than the general concepts, which are admirably emphasised.

The chapter on blood-group substances is an extremely clear exposition of a difficult subject. The section on inherited serum-proteins, however, is a little sketchy. There is no mention of the inherited variation in serum-albumin, first described in 1957, in which serum-albumin is present in two distinct molecular species (" double albumin "), nor indeed of certain other inherited serum-proteins, some of which have been recently described by Dr. Harris. Unavoidable delays in publication are no doubt largely responsible. The beta-globulin variants are now recognised as transferrins, and the account of inheritance of the gamma-globulin groups will have to be expanded considerably in later editions. The current and lively topic of the genetic aspects of antibody formation is not discussed, and surprisingly no reference is made to the contributions of Beadle and Tatum, whose work in biochemical genetics, albeit in species other than man, has been outstanding. Dr. Harris has remained strictly within his title, and some readers would perhaps have liked at least an occasional reference to species other than man.

Nowhere are the disciplines of biochemistry and clinical medicine more closely linked than in the conditions discussed here, and we hope this book will reach the desks of all biochemists concerned with the teaching of medical students. The author might have permitted himself the luxury of a little more speculation: he does not, for instance, discuss in any detail the possible ways in which alteration of the base sequences in D.N.A. can give rise to altered proteins. We find little or no mention of coding mechanisms, soluble R.N.A., or ribosomes; but these are small points. Only a few misprints were noticed in a book which successfully combines sound production with modest price.

There is no doubt that this is the best book on human

biochemical genetics available today. Dr. Harris is to be congratulated on a much needed work well done: it can be warmly and unreservedly recommended.

Water Supply for Rural Areas and Small Communities

E. G. WAGNER, chief engineer, division of health and sanitation, Institute of Inter-American Affairs, Rio de Janeiro; J. N. LANOIX, sanitary engineer, division of environmental sanitation, W.H.O., Geneva. World Health Organisation Monograph Series no. 42. Geneva: W.H.O. (Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.) 1959. Pp. 340. 35*s*.

THOSE who first urged a clean water-supply may have been stirred by irrational emotions derived ultimately from J. J. Rousseau, but they did as much for the public health as all the bacteriologists put together. We turn on the tap and accept their bounty without question. To us typhoid and other water-borne infections are no more than rare curiosities. Most of the world's inhabitants are, however, still countrymen who lack piped water, main drainage, and electricity—and of these the first is the most important by far. One of the happiest pages in the history of our rule in India is the effort made to give the villager a "safe" well; and now almost everywhere clean water has a top priority.

This book is a model for what such publications should be. It is practical and inclusive and cheap. In it anyone from Iceland to Peru can find plain directions for the choice, impounding, and purification of any sort of available water: he can get some idea of the cost of building and working the supply and the staff which will be needed. The book may emanate from Geneva, but the authors know from personal experience that most wells are still dug with pick and shovel or mattock and the earth removed in a basket on a rope.

The book fills a need even in this country. Few medical officers of health have had the opportunity to learn much about emergency water-supplies, and circumstances could arise in which these would have to be improvised amid wreckage and confusion.

J. M. Charcot, 1825-1893

His Life—His Work. GEORGES GUILLAIN, M.D. Edited and translated by PEARCE BAILEY, PH.D., M.D., director, National Institute of Neurological Diseases and Blindness, Bethesda, Maryland. London: Pitman Medical Publishing Co. 1959. Pp. 202. 50*s*.

THOSE Parisians who lived within the ramparts of the old city during the middle of the sixteenth century were so often disturbed by violent explosions in the royal arsenal that they petitioned Louis XIII to store his gunpowder elsewhere. In 1565 he acceded to their request, and erected another arsenal on the opposite bank of the Seine. In later years these buildings were much enlarged, and came to be used as an infirmary, at first for destitute women and prostitutes, and then for the chronic sick, the crippled, and the insane. At times this "grand asylum of human misery" housed as many as 8000 patients, some under appalling conditions. The work of such men as Pinel, Magendie, and Cruveilhier did much to ameliorate and to enhance the reputation of the Salpêtrière (as the institution continued to be called). But it was the appointment, in 1862, of Jean Marie Charcot, as its chief of the medical service, which was destined to make it a Mecca of doctors the world over.

A modern physician, as Professor Guillain points out, finds it hard to appreciate the debt neurology owes to Charcot. When he began his work at the Salpêtrière, scarcely anything was known of the pathology of nervous disease: the methods of clinical examination in common use were rudimentary and ineffective: and such terms as "tremor" and "paralysis" were regarded as constituting a sufficient diagnosis in themselves. One half of this book describes in considerable detail the publications and researches by which Charcot raised the whole status of our knowledge of diseases of the central nervous system: the other is devoted to a personal biography. Though its author never met Charcot, he is senior enough to have known many of his pupils and friends, and his book is an important contribution to our knowledge of a man who has not hitherto received from biographers the attention he deserves, as the Father of Neurology.

Recent Progress in Psychiatry

Vol. 3. Editors: G. W. T. H. FLEMING and A. WALK. London: J. & A. Churchill. 1959. Pp. 397. 42*s*.

THIS volume is the third in the deservedly well-known series sponsored by the Royal Medico-Psychological Association (others appeared in 1944 and 1950) and the contributions live up to a distinguished tradition. Since many relevant advances have been made in related disciplines, clinical chapters are rather fewer, and the condensation of a vast area (nearly 2000 references are covered) makes for hard reading in places, although Prof. Alexander Kennedy and Dr. F. J. Fish, for example, writing on addiction, and Dr. R. Gibson on mental deficiency, show that brief but extensive surveys can be both scholarly and easy to read. Other topics authoritatively covered are surgical treatment (Mr. M. A. Falconer and Mr. Peter Schurr), child psychiatry (Dr. Kenneth Cameron), major crime (Dr. Jonathan Gould), and genetics (Dr. Valerie Cowie and Dr. Eliot Slater). More abstruse are biochemistry (Dr. Derek Richter), enzymes (Dr. Gould), the physiology and pathology of cerebral structures (Dr. T. P. S. Powell, Dr. J. A. N. Corsellis, Dr. Alfred Meyer, Dr. R. M. Norman, and Dr. Henry Urich), cybernetics (Dr. W. Ross Ashby), and personality testing (Prof. H. J. Eysenck). A name index, an ampler subject index, and prompter publication (the most recent papers quoted are 1956) might be possible for the next volume.

In his introduction Dr. Fleming declares:

"Modern psychiatry is passing through a period of apparent change. The law relating to mental illness has come under considerable criticism, some of it from the unstable and hysterical. This has led to changes in administrative outlook which are certainly not always in the best interests of the patient, his relatives, or the public, but bolster up the ego of the inferiority unconscious psychiatrist. Amongst the inexperienced there is an impression that what they are doing has never been done before, and they either make no attempt to ascertain how much was done twenty and more years ago, or turn a deaf ear and a blind eye."

If one of the objects of this sharp passage is to restrain over-enthusiastic zeal for reform it should surely have been more sympathetically worded. As it stands it can hardly fail to sour the atmosphere: what is needed by young and inexperienced enthusiasts (of whom there seem to be too few by our reckoning) is guidance and encouragement.

Fundamentals of Gynecology

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THIS new book by two American teachers is based on the lecture course in gynæcology at the University of Michigan Medical School and is designed for senior students and general practitioners. It gives a lucid, well-ordered account of modern gynæcology, in which the British viewpoint is well represented. The general layout of the material is sound and the exposition clear. The publishers deserve special credit for the excellent production.

Each chapter is a short, balanced, and authoritative monograph on some division of gynæcology. At the end of every chapter there are appropriate references, British and American, to which the reader may turn for more detailed information. The chapters on Virilism and Intersexuality in the Female, Endometriosis, and Hydatidiform Mole and Choriocarcinoma are especially valuable; and the whole section on malignant disease is very effective, though conceivably it might be improved by more detail about the place of cytology in the early diagnosis of cancer of the cervix. The text is well illustrated by diagrams, photographs, and drawings, but occasionally the photomicrographs are too small for detail to be seen.

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The Report

THE Royal Commission remark ruefully that their task was expected to be simple but proved otherwise. Though they have listened patiently to a great many suggestions for improving the National Health Service, they have had to resist any temptation to solve all its problems. But their recommendations, though mainly monetary, reflect well-founded and friendly opinions, on the profession and the service, for which we can be thankful.

Some things that people told them, they do not accept: they are not bothered about medical emigration, for instance, or a decline, so far, in recruitment. They flatly declare, too, that remuneration can no longer be governed by the Spens reports. As basis for their own conclusions they have collected a mass of new information about medical and other incomes, from which they conclude that medical earnings are too low. But they also add opinions which reflect their experience in other branches of life—notably that the young doctor is relatively underpaid, that the range of incomes should be wider, and that special distinction—in general practitioners as well as in consultants—needs financial recognition. Promotion and differential remuneration are never quite equitable, in any organisation; but on the whole the system works. The Commission find it hard to believe that Medicine alone has a complete lack of "that selective ability which is exercised in practically all other occupations". Not without humour, they suggest that their proposed fund of £500,000 a year, set aside for recognising distinguished general practice, shall revert to the Exchequer if not used.

For consultants, distinction awards should, they think, be higher but limited in number; and substantial rises of pay are proposed for all hospital staff. Leaving to the Platt Working Party the question of hospital grades, the Commission do little to solve the registrar problem except that they leave senior registrars on a rising scale for a longer time. Their most important change of relativities lies in the higher pay for registrars, senior house-officers, and particularly house-officers, who "have been greatly underpaid both in relation to their seniors and in relation to what is paid to comparable people in other professions". Whereas elsewhere the Commission's rates are a little lower than those suggested by the British Medical Association, for the house-officer they are higher. Another recommendation designed to help peripheral hospitals would entitle these to pay an additional £100 a year to junior staff.

The Commission's proposals for general practice are preceded by a masterly review of the practitioner's present situation. They would retain capitation fees, and the pool; and, though the amount to be put into this for each doctor would be raised only to £2425, they say that, with changed methods of calculating the pool, this would mean an average increase of £450 over 1955–56. Professor JEWKES, in an impressive memorandum of dissent, argues that this increase, like that suggested for part-time consultants, is too low either to restore confidence or to ensure recruitment: he says that unless practitioners' remuneration is now raised by at least 30% over that ruling in 1955–56, their position will have deteriorated during the decade in relation to that of other people. On reduction of the maximum list the Commission do not commit themselves: whatever is decided about this, they are anxious that a wide range of incomes shall be achieved—the distinction award being one possible means. "We do not believe that constant striving for increased income is or should be the main incentive to good general practice, but at the same time we think it must be discouraging both to existing doctors and to potential recruits if a really first-rate practitioner has so little prospect of earning more than one who is merely satisfactory". Again urging better pay for the young, they are generous to the trainee assistant. Other assistants, they hope, will benefit too, though less directly.

Even more important than what is paid in 1960-63 is what happens later. We are all painfully familiar now with the type of Government economy which asks disproportionate sacrifice from people who happen to be paid from public funds; and we are grateful both for the Commission's acid statement that "doctors and dentists must have some confidence that their remuneration will be settled on a just basis" and for their declaration that "doctors and dentists in the public service should not be used as a regulator of the national economy". To review major issues periodically, the Commission propose a standing Review Body, of seven independent persons, to advise the Prime Minister. (Professor JEWKES, who evidently shares our wish for more strategic planning of the Health Service, would like to see this develop into an Advisory Council.) The Commission remark, again rather pointedly, that the recommendations of the Review Body "must only very rarely and for most obviously compelling reasons be rejected". Their request that £11 million shall now be paid to general practitioners, and £9 million to hospital doctors and dentists, in respect of the time elapsed since the inquiry began in 1957 is evidence that they do not regard the profession's repeated protests as baseless. We earnestly share their hope for an end, once for all, to the damaging disputes of the past.

Hæmorrhoids

"NATURE is not infallible," Saki's major observed, "but she usually abides by her mistakes." Whether they are inborn flaws or signs of imperfect adaptation, a host of minor ailments that beset us after the age of twenty seem to support his contention. Hernias, varicose veins, slipped discs—all carry an excellent prognosis for life and a tolerable one for comfort, but the chances of complete cure are often remote. By most published accounts hæmorrhoids—perhaps the most important member of this group—are the exception, for they are said to be eminently curable. But are they in fact? The truth about hæmorrhoids is not easily discovered: to many doctors they remain an unexciting and to most patients a faintly embarrassing complaint. And yet these patients form a large proportion of chronic bleeders; and chronic bleeders, with their lowgrade but intractable iron-deficiency, should be one of our pressing concerns. Neither ill nor well, unable to cope with their work and incapable of enjoying their leisure, these men and women become, in the prime of their lives, a trial to themselves and an unrecognised burden on the community. They also become the worst of patients—truculent in seeking advice, erratic in following it, always ready to take their own discharge once in hospital. It is hardly surprising that many are fobbed off by their doctors with iron—any old iron—at an early stage of their illness and thus find themselves launched on a vicious circle of bleeding, iron-deficiency, increasing istrogenic constipation, more bleeding, and worse iron deficiency. Even spontaneous remissions are not an unmixed blessing, for they promote indiscriminate claims made for a bewildering variety of patent "anti-hæmorrhoidals"—some so extravagant that they could hardly be expected to sell were prospective buyers' critical faculties not blunted by a hæmoglobin of 60%.

The rational management of hæmorrhoids, like that of most common but not life-threatening illnesses, calls for a compromise between the ideal and the workable. To preach prophylaxis, tracing back the condition to bad bowel-habits inculcated in childhood, is hardly practical; nor is it realistic to suggest (as some textbooks do) that every case of rectal bleeding should be investigated not only clinically but also hæmatologically and radiologically. Isolated episodes in young people are extremely common and usually of no significance: intelligent assessment of the history and a brief general and careful rectal examination is all that they require. If the bleeding recurs, however—and before embarking on surgical treatment—at least two common underlying causes must be excluded. The spectre of hæmorrhoids masking carcinoma of the rectum so effectively haunts most newly qualified doctors that their elders are more likely to offend. Less widely appreciated is the common association between non-specific proctitis (with or without hæmorrhoids) and rectal bleeding; and, even when remembered, the diagnosis may tax the most experienced.

When a serious underlying disease has been excluded, a course of injections can be confidently recommended for grade-1, grade-2, and even some grade-3 hæmorrhoids—provided that emphasis is laid on the "course". Proctologists often deplore that the average patient, delighted by even a temporary respite, is not urged by his general practitioner to attend a second and third time; but proctologists themselves are not entirely blameless. In skill, hygiene, and efficiency the special clinics which are now run by most hospitals have been a great advance on the old system of seeing rectal cases in general surgical outpatients; but all too often increasing efficiency generates an unwholesome conveyor-belt spirit. Clad in gaily coloured but ill-fitting dressing-gowns patients are marched by sister into grim little cubicles, instructed to hop on a couch, and reduced into a position which can demoralise the toughest; and after an anxious wait (which might have served as RODIN'S inspiration for his *Danaïde*) they may find themselves impaled on a sigmoidoscope without having set eyes on the surgeon. Inflated, injected, and thoroughly intimidated, most of them are yet grateful for the relief afforded by the treatment; but their disinclination to attend again is not perhaps to be wondered at. Serious complications from injections are oddly few: potentially perhaps the gravest, as also the most insidious, is hepatitis from intravenous phenol.

For hæmorrhoids which recur after two or three courses of injections and for most grade-3 cases well-conducted hæmorrhoidectomy is thoroughly worth while; but what a "well-conducted hæmorrhoidectomy" means has been disputed almost since the dawn of surgery. The results from the clamp-and-cautery operation, as described by FARQUHARSON,[1] and from the St. Mark's Hospital dissection-ligature operation [2] have been compared by CORMIE and MCNAIR [3]; and their findings shed light on the late results of surgical treatment in general. 163 consecutive patients who had been treated in one unit of the Edinburgh Royal Infirmary by one of the two operations were circularised by letter: and 100 were available for reassessment. After an average of four and a half years only 65 could be classified as "excellent" results; but the criteria were strict, and "no less than 94 of the 100 patients were either cured or were improved to the degree of suffering from only minor occasional symptoms. All these patients were in no doubt about the merits of the operative treatment and many expressed the wish that they had come at an earlier date and so saved themselves many years of discomfort." On the other hand, it is perhaps not unreasonable to assume that (apart from 10 who had died from other illnesses since the operation) the 53 who could not be traced or who could not attend may have included a larger proportion of dissatisfied patients; nor would a five-year follow-up include late recurrences. Immediate complications were few after either operation: only 1 patient had a hæmorrhage, and this responded to conservative measures.

1. Farquharson, E. L. Textbook of Operative Surgery. Edinburgh, 1954.
2. Milligan, E. T. C., Morgan, N. C., Jones, L. E., Officer, R. *Lancet*, 1937, ii, 1119.
3. Cormie, J., McNair, T. J. *Scot. med. J.* 1959, **4**, 571.

(HUGHES [4] reported 3 cases of this, potentially the most serious, complication in a series of 221 cases.) Post-operative retention, regarded by some as almost inevitable, was rare in both groups; but pain and discomfort were strikingly less after the clamp-and-cautery procedure. CORMIE and MCNAIR recognise that this may reflect small individual differences in technique (such as the use of a flatus tube instead of petrolatum-jelly on soft dressings); but conceivably the linear scars of the cautery are in themselves less painful than the raw surfaces left after dissection and ligature. Of the late complications stricture-formation is the one most dreaded; and, especially when not recognised in time, it can indeed be a disaster. In the Edinburgh series mild stenosis was slightly commoner after the St. Marks' Hospital procedure; but such stenosis can follow any operation (and even misplaced injections) and probably results from some error in technique. The need for a "tidy" end-result is doubtful: skin-tags are usually symptomless but commoner when the cautery has been used. Chronic fissure-in-ano—a far more troublesome sequel—appears to have developed in about the same proportion of the two groups.

What emerges from the Edinburgh and similar surveys is that, good though the results are, there is scope for improvement at all stages of the illness and all levels of its management. Hæmorrhoids are said to have been one of the three essential adjuncts and afflictions of the successful Victorian physician. A paunch was his hallmark of well-merited affluence, baldness gave him an air of experience and wisdom, and hæmorrhoids ensured a look of constant anxiety. We can pride ourselves of having shed both the substance and the meaning of the first; we are casting doubt on the interpretation of the second; but we remain faithful to the third. Hæmorrhoids is still a disease of the professional classes: it deserves the interest—but is often accorded the neglect—of a doctors' ailment.

Fifteen Years of Antibiotics

IN 1945 the only antibiotic available for systemic use was penicillin: today there are about fifteen. How then do we stand? So wide a question demands a comprehensive answer; and we are fortunate that this has been given in a valuable issue of the *British Medical Bulletin*,[5] edited by Prof. L. P. GARROD, which contains fifteen articles by eighteen other experts. If all users of antibiotics read and understood these articles there would surely be a great increase in the efficacy of antibiotic treatment combined with a striking reduction in the number of patients given antibiotics, the number of undesirable complications, and the number of antibiotic-resistant strains of bacteria. It is not possible for anyone—or any Government agency—to utter a series of commandments on the use of antibiotics, because there are important aspects of the subject about which it is not yet possible to dogmatise. But clearly an antibiotic is often given without a clear enough reason in the mind of the doctor prescribing it. True, what begins as a minor illness not apparently requiring an antibiotic may develop into something more if it is not treated, whereas it may respond admirably if it is treated. As GARROD and SCOWEN [6] say: "Each case must be judged on its merits, but if these are deliberately assessed, and if the treatment has an explicit rational basis, really indiscriminate use will thereby be excluded."

Clinicians are not slow to emphasise that they know of cases in which a laboratory report on the sensitivity or resistance of an organism to a particular antibiotic did not correlate well with the patient's response to treatment with that drug. This observation is often enough correct, and there are at least seven possible explanations for it: (1) an effective antibiotic may be unable to reach a sensitive organism (in dead tissue or pus, for example); (2) if infection is secondary to obstruction or stasis, in the urinary tract or elsewhere, the effect of any chemotherapy will be only temporary unless the underlying condition can also be relieved; (3) special conditions may be needed for an antibiotic to act (streptomycin, for example, is about 50 times more active in an alkaline than in an acid urine, whereas penicillin and chlortetracycline are more effective in an acid medium); (4) the antibiotic may be diluted beyond the point of effectiveness (a mischance especially probable in urinary infections because these patients are traditionally urged to drink all they can, whereas restriction of fluids for a time is necessary to secure the greatest possible concentration of the drug in the urine); (5) resistance of an organism to a particular antibiotic, reported by the laboratory, does not hinder natural recovery from an infection which would resolve without chemotherapy; (6) the sensitivity of the culture tested in the laboratory may differ from that of the organism in the patient's tissues; and (7) circumstances may sometimes allow the attainment of concentrations of antibiotic in the tissues greater than those normally to be expected. Despite discrepancies of this kind, GOULD [7] leaves no doubt about the important part which the laboratory should play in assisting chemotherapy; for clinical diagnosis is not often a dependable guide to the identity and antibiotic sensitivity of the infecting organisms. Further, the laboratory may help in measuring the efficacy of treatment and aid the clinician in his decision when he may safely stop it.

LOWBURY,[8] discussing possible measures to combat the emergence of drug-resistant pathogens, evaluates discriminating restraint in the use of antibiotics, prevention of hospital infection, well-chosen combinations of drugs for a few special infections, and agreed schemes for the use of antibiotics in rotation—a change being made as soon as, or preferably before, drug-resistant strains of bacteria appear. He rates attempts to prevent cross-infection as probably the most important, but finds better hopes in some of the newer antibiotics than seemed at all likely a few years ago. Some of these new drugs are too toxic for parenteral use; but others are not

4. Hughes, E. S. R. Surgery of the Anus, Anal Canal and Rectum. Edinburgh, 1957.
5. Antibiotics in Medicine. *Brit. med. Bull.* 1960 **16**, 1–85.
6. Garrod, L. P., Scowen, E. F. *ibid.* p. 23.
7. Gould, J. C. *ibid.* p. 29.
8. Lowbury, E. J. L. *ibid.* p. 73.

—although, in general, the treatment must be conducted with a sharp watch for toxic signs and a resolve not to overdose the patient or unnecessarily prolong the treatment. Usually combinations of drugs are needed for the treatment of tuberculosis and subacute bacterial endocarditis caused by enterococci. BARBER et al.[9] showed that the combination of novobiocin and erythromycin apparently prevented the emergence of resistant strains, whereas the combination of chloramphenicol and erythromycin should be avoided because of cross-resistance between the two drugs. Obviously, the use of antibiotics in combination requires much more critical thought and study than it has yet received. It is a relief that the uncritical enthusiasm for combinations which was notable a few years ago appears to have abated.

The enterprise of those who have pioneered the development of antibiotics has been notably supplemented, to the benefit of all, by the outstanding efforts of the pharmaceutical industry. Understandably the industry wishes to have a reasonable financial return; but probably all of us, including the industry, would be happier if the over-enthusiastic reports of uncritical users of some of the new preparations were carefully, realistically, and even sceptically assessed before they were allowed to exert any great influence on sales policy.

Annotations

ESCHERICHIA COLI IN PETS

A FEW weeks ago we called attention to the dangers of keeping dogs, and indeed of having anything at all to do with them.[10] Now a further possible hazard has been revealed. Mian,[11] working in Michigan, examined 321 household pets and found serotypes of *Escherichia coli* known to be associated with infantile enteritis in 14% of dogs and 8% of cats. Furthermore in one instance he detected the same serotype (O 55 : B5) in a child with diarrhœa and in a dog in the same house (the possibility that the baby infected the dog does not seem to have been considered).

Knowing the almost indecent intimacy which many pet-lovers allow their furry friends, we are not surprised; and yet we feel bound to accept this warning with some caution. There is no longer any doubt that certain serotypes of *Esch. coli* cause enteritis in children under 2 years and occasionally in older people; but the same serotypes are also found not uncommonly in apparently healthy persons of all ages. No-one has brought forward very convincing evidence that babies are infected by their mothers or vice versa. "Scouring" in calves deprived of maternal colostrum is also caused by certain serotypes of *Esch. coli*. Some of these are identical with those implicated in human disease, and it was thought at one time that cow's milk was an important source of human infection. In recent years, however, the serotypes prevalent in calves and babies have not been the same, and indeed one of the most interesting things about these diseases is the changes over the years in the types most commonly associated with human and bovine disease. In this country types O 55 and O 111 have largely given way to O 26 and O 119 in babies, while in calves O 78 and O 137 have displaced O 9, O 26, and O 35. Other serotypes—some shared with humans and calves—have been found to cause enteritis in lambs and various ailments in piglets.[12] It is a reasonable guess that all young animals are liable to these infections, but whether the disease in one species has any relation to that in another we do not yet know. Incidentally some of these pathogenic serotypes have been found in well-water.

This epidemiological problem is confusing. Interest in the enteroviruses has encouraged the idea that enteric disease in the young is due to one or more viruses and that the "pathogenic" serotypes of *Esch. coli* are normal inhabitants of the upper bowel flushed down by viral diarrhœa. (In current medical conversation "virus infection" is likely to mean "a disease of uncertain ætiology".) Yet recognisable enteroviruses are rarely if ever found in patients with diarrhœa who are excreting any of the specific serotypes of *Esch. coli*.[13] For the moment we must accept that these are the cause of the disease, and yet clearly the epidemiology of "coli enteritis" differs quantitatively if not qualitatively from such infections as typhoid fever or Sonne dysentery. The number of symptomless excreters—"carriers" begs too many questions—is far greater, and yet when the disease spreads in a children's ward it is highly infectious and persistent. In some well-run hospitals the disease is almost always present: in others, a few miles away, only occasional sporadic cases are seen.

We hope that others will repeat Mian's work and compare their findings with those of the local hospital. The origin of single infections is always obscure, and domestic pets are as likely a source as any. It is true that not much has come of the observation that about 3% of dogs carry *Salmonella spp.*, but perhaps this lead has not been pursued with enough vigour. At any rate these findings give the family doctor yet another reason to discourage dogs from sleeping on beds or licking the baby.

AUTOMATION

AUTOMATION—a threat to the community or a panacea? Whatever its advantages it clearly raises problems, including problems of mental health; and W.H.O. has published the report of a study group which considered this aspect.[14] The study group point out that automation may be broken down into three overlapping types: "transfer automation" of the assembly-line type now long familiar; "control automation" based on automatic feedback of information into a mechanical system; and "computer automation", the most revolutionary, used most commonly in the recording, coordination, and analysis of information for administrative purposes. Automated work may affect the functioning of operators, and therefore possibly cause mental ill health, through increased responsibility without action to provide relief, through the need for close attention without adequate motor discharge, through solitariness, and through "depersonalisation". The need to react almost instantaneously to alarm signals is a particular strain, which may be alleviated by rational grouping of indicators and the presentation of useful information only. Adequate changes of position and good general environmental conditions are also important. The effects of excessive isolation and absence of social contact are compared with

9. Barber, M., Csillag, A., Medway, A. J. *Brit. med. J.* 1958, ii, 1377.
10. *Lancet*, 1959, ii, 1017.
11. Mian, K. A. *J. Amer. med. Ass.* 1959 **171**, 1957.
12. Rees, T. A. *J. comp. Path.* 1958, **68**, 388, 399; *ibid.* 1959, **69**, 334.
13. Young, V. M., Warren, J., Lindbergh, R. B. *Proc. Soc. exp. Biol., N.Y.* 1959, **100**, 579.
14. Mental Health Problems of Automation, *Wld Hlth Org. tech. Rep. Ser.* 1959, no. 183. Obtainable from H.M. Stationery Office, P.O. Box 569. London, S.E.1. Pp. 30. 1*s.* 9*d.*

those of " sensory deprivation ", which may be profoundly disturbing.[15] These effects may be avoided by reducing noise level, placing machines suitably, shortening shifts, increasing breaks during working hours, and a system of flexible rotation.

The study group stresses that automation is likely to bring important advantages. It should enable working conditions to be improved, and in the long run lead to reduction of working hours and an increase in the trend towards better wages. People should not be confronted with the new type of life associated with automation without adequate information and education; this is particularly important for those holding key positions. There is still much to be learned about the impact of automation on the individual and society.

BLOOD-AMMONIA AND EMPHYSEMA

RAISED blood-ammonia levels may be found in association with advanced liver disease, and they have also been observed in states of shock,[16] congestive heart-failure,[17–19] and diabetic coma.[20] Recently Dutton et al.[21] reported high blood-ammonia levels in patients with chronic pulmonary emphysema unassociated with congestive heart-failure, and they now amplify [22] their original observations. They studied 34 patients with chronic pulmonary emphysema, none of whom had clinical evidence of congestive heart-failure or liver disease and none of whom were receiving drugs known to influence blood-ammonia levels. Bromsulphalein tests of liver function were carried out in 28 of these patients, and comprehensive tests of lung function in 12. The mean venous blood-ammonia value for the 34 patients with emphysema was 52 *u*g. per 100 ml., and that of a control group of 37 patients was 26 *u*g. per 100 ml.; the figure for the emphysematous subjects was thus significantly higher ($P < 0{\cdot}01$). The 12 patients whose lung function had been intensively studied were classified into three groups according to the results of blood-gas analysis after standard exercise [23]: in group 1 arterial oxygen saturation was above 92%; in group 2 arterial oxygen saturation was below 92% and arterial CO_2 tension below 48 mm. Hg.; and in group 3 arterial oxygen saturation was below 92% and arterial CO_2 tension above 48 mm. The blood-ammonia levels were normal in the 3 patients in group 1, and raised in the 7 patients in group 3; they were normal in 1 of the patients in group 2 and elevated in the other.

Dutton et al. do not find it easy to account for the abnormal blood-ammonia levels in these patients with pulmonary insufficiency. A rise in blood-ammonia may be due to impaired ability of the liver to convert ammonia to urea, but no evidence of liver disease was detected. Portapulmonary and thoracic portacaval venous anastomoses may exist in the absence of portal cirrhosis,[24] but Dutton et al. consider it unlikely that blood would have passed into the systemic circulation through such channels even if they were present in their cases, because of the raised intrathoracic pressure associated with the pulmonary disease. Since muscle activity has been reported to raise blood-ammonia levels,[25] it seemed possible that increased respiratory work might explain the rise in the emphysematous patients; but the absence of any rise of blood-ammonia in 2 healthy subjects who increased their ventilation to many times the normal value lent no support to this hypothesis. On the whole, they think the likeliest explanation is that chronic hypoxia impairs the ability of the liver to metabolise ammonia, and that this defect is not necessarily reflected in the results of the bromsulphalein test. Hyperventilation observed in patients in early hepatic coma has been thought to be due possibly to the action of high blood concentrations of ammonia on the respiratory centre [26 27]; and Dutton et al. suggest that in pulmonary emphysema with carbon-dioxide retention a high blood-ammonia may be a factor additional to arterial hypoxia in stimulating respiration.

SCHOOLS AND INFECTIOUS DISEASES

THE bedevilment of medicine by ex-cathedra statements has seldom been better illustrated than by W.H.O.'s examination [28] of current practice in excluding children from school because of infectious disease. This survey is based on legislation and recommendations in one Asian, three Australasian, eight European, two African, and four American countries or States. Surprisingly no reference is made to *Control of Communicable Disease in Man*, the official report of the American Public Health Association. It is understandable that different countries issue different rules which vary widely, but, to add to the confusion, individual cantons in Switzerland and States in America and Australia have their own laws, and in England the Ministry of Education and the Medical Officers of Schools Association have differing practices. No wonder the W.H.O. report concludes that any country wishing to introduce new regulations will get no real guidance from a study of existing conditions. Nevertheless there is without doubt a firm trend towards surveillance rather than exclusion, and the child who is known to be naturally immune or to have been immunised is usually allowed to go to school. Perhaps the most pleasing feature is that in several countries rubella is recognised as a disease for girls to have before they are likely to become pregnant.

France, justly proud of the part played by Ramon in perfecting diphtheria immunisation, excludes from school children who have had the disease for 30 days after a clinical cure or until 8 days after two negative cultures. Contacts if immunised are allowed to go to school, but if not they are excluded for 15 days. Carriers are excluded until a medical certificate is produced. The management of diphtheria in France is a good example of how to take advantage of recent advances, and this policy should encourage active immunisation.

It is surprising to find that there is virtually no uniformity whatever in the measures prescribed for schools to deal with diseases whose epidemiology, evolution, and method of spread are well known. The only positive point that emerges from this study, when compared with the

15. *Lancet*, 1959, ii, 1072.
16. Nelson, R. M., Seligson, D. *Surgery*, 1953, **34**, 1.
17. Bessman, A. N., Evans, J. M. *Amer. Heart J.* 1955, **50**, 715.
18. Austen, F. K., Carmichael, M. W., Adams, R. D. *New Engl. J. Med.* 1957, **257**, 579.
19. Conn, H. O. *ibid.* 1958, **259**, 564.
20. Fuld, H. *Klin. Wschr.* 1933, **12**, 1364.
21. Dutton, R., Jr., Nicholas, W., Fisher, C. J., Renzetti, A. D., Jr. *Clin. Res.* 1958, **6**, 316.
22. Dutton, R., Jr., Nicholas, W., Fisher, C. J., Renzetti, A. D., Jr. *New Engl. J. Med.* 1959, **261**, 1369.
23. Baldwin, E. de F., Cournand, A., Richards, D. W., Jr. *Medicine*, 1948, **27**, 243.
24. Calabresi, P., Abelmann, W. H. *J. clin. Invest.* 1957, **38**, 1257.
25. Schwartz, A. E., Laurence, W. Jr., Roberts, K. E. *Proc. Soc. exp. Biol., N.Y.* 1958, **98**, 548.
26. Vanamee, P., Poppell, J. W., Glickman, A. S., Randall, H. T., Roberts, K. E. *Arch. intern. Med.* 1956, **97**, 762.
27. Roberts, K. E., Thompson, R. F. G., III, Poppell, J. W., Vanamee, P. *J. appl. Physiol.* 1956, **9**, 367.
28. Communicable Diseases in Schools: a Survey of Existing Legislation. Geneva: World Health Organisation. London: H.M. Stationery Office. Pp. 65. 3*s*. 6*d*.

conclusions drawn from corresponding work in 1952, is that there is a tendency to reduce the stringency of exclusion measures for both patients and contacts.

DEFORMITIES OF LONG BONES

IN children severe deformities of the long bones associated with generalised skeletal disturbance tend to be progressive, and to recur under the strain of weight-bearing or even of muscle action. Sofield and Millar [1] have long used a method of fragmentation and realignment of the deformed long bones.

With deformity of the femur the operation involves subperiosteal exposure of the entire shaft with osteotomy through the proximal and distal metaphyses. The isolated shaft is divided into 2, 3, or 4 pieces, which are removed and threaded in the most appropriate order along an intramedullary rod which passes into the intact ends of the bones. Reconstitution of the femur is rapid, but growth of the epiphyses away from the rod leaves a new part of the shaft which may bend or fracture at its junction with the intramedullary pin. A longer pin may have to be introduced, the end of the bone being realigned upon the rod.

This method has also been used in the treatment of congenital pseudarthrosis of the tibia, although here its virtues are not so great. In view of the stimulation of growth by fracture of the long bone, Sofield and Millar have extended their fragmentation procedure to the treatment of the short leg. But, as with other methods which rely on the stimulation of growth by periosteal raising or by fracture, the gain in growth seems to be slight and inconstant.

SPREAD OF STAPHYLOCOCCI FROM HOSPITAL TO COMMUNITY

THE danger to the public when "hospital" staphylococci are taken home by patients is not always appreciated, even by doctors. Many workers have shown that this does occur—that the community is being infected by strains, usually highly virulent, which are selected by virtue of their resistance to the common antibiotics.[2–8] Wentworth et al.[9] describe an investigation in which 1287 babies were seen at home between one and five months after birth. There was staphylococcal disease in 45% of the 435 families in which the babies had been infected when they left hospital, but in only 9·5% of the families where the babies had been clinically free from infection. 26 babies left the hospital carrying the epidemic strain; and about five months later three-quarters of the mothers and a third of the other members of the family were found to be carrying the same strain, while 8 mothers, 3 fathers, and 8 siblings had developed actual staphylococcal lesions.

Boils and abscesses can cause a great deal of pain and inconvenience, but there are two groups of people for whom contact with a "hospital" staphylococcus may be more serious. The first are children under 2 years of age, who are particularly susceptible to staphylococcal pneumonia: this is described by Morris [10] as now one of the commonest serious diseases in pædiatric practice, whereas formerly it was rare. It is difficult to diagnose and rapid and severe in its course. Isbister [11] has reported 22 cases, of which 6 were fatal; 17 could be traced to hospital infection—2 occurred in toddlers whose mothers had just returned from maternity hospitals with a new baby (and a staphylococcus). The second type of patient who is in particular danger from the hospital-derived staphylococcus is the one with influenza. Goslings et al.[12] in Leiden sought a history of staphylococcal infection in the families of 40 patients whose influenza was complicated by staphylococcal pneumonia. In a third of this group identical organisms were isolated from the sputum and from skin lesions, which were found more often in family contacts than in the patients themselves.

Obviously, the most important way to prevent this spread of virulent staphylococci to the community is to clear the organisms from our hospitals—particularly the maternity units. The search for methods of doing this continues.[13–15] One method which seems to be of particular value is the application of hexachlorophane, as an emulsion [16] or a powder,[17] to areas of babies' skin where staphylococci grow most prolifically.

Another way of approaching the problem is to make certain staphylococcal infections notifiable. We have not the same problem here as in America, where mother and baby leave hospital four or five days after delivery, and where the majority of hospital-acquired infections become manifest at home. Thus, in the U.S.A. the original outbreak may be missed,[14] and only appreciated afterwards because of the large number of readmissions. But we must look out for the more severe infections, such as breast abscess, empyema, pneumonia, and osteomyelitis, which take several weeks to develop. At the moment there is no way of establishing the incidence of these or of tracing them back to the hospital of origin. A British Medical Association committee [18] reporting on possible changes in notifiable diseases recognised this defect by proposing compulsory notification of any coccal disease of a child or mother within twenty-one days of delivery. In New South Wales the notification of staphylococcal mastitis, pneumonia, and infections of infants under 4 weeks old is now compulsory. There are certain difficulties about this [17]—difficulties, for example, of definition and of diagnosis. Isbister [11] considers that the time limit of four weeks is too short, as she has found that most of the really dangerous complications develop after the neonatal period. Some form of notification is essential, if only to make us aware of the extent of the problem.

At this season it is especially important to appreciate the danger to an influenzal patient if there is a staphylococcal infection in the family. The antibiotic-resistance pattern of the organism should be discovered as soon as possible, and penicillin and the tetracyclines should be withheld unless the staphylococcus is known to be sensitive to them. Most "hospital" strains are not.

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Special Articles

REMUNERATION OF DOCTORS AND DENTISTS

Royal Commission's Report

THE Royal Commission on Doctors' and Dentists' Remuneration was appointed in 1957 with Sir Harry Pilkington as chairman. Its report, signed by all but one of its members, has been issued this week.[1] The commission finds that the present remuneration of doctors is inadequate; and it proposes the establishment of machinery to keep remuneration under review.

The commission was appointed to consider:

1. How the levels of professional remuneration from all sources now received by doctors and dentists taking any part in the National Health Service compare with the remuneration received by members of other professions, by other members of the medical and dental professions, and by people engaged in connected occupations;
2. What, in the light of the foregoing, should be the proper current levels of remuneration of such doctors and dentists by the National Health Service;
3. Whether, and if so what, arrangements should be made to keep that remuneration under review;

and to make recommendations.

GENERAL OBSERVATIONS

The report opens with five important general observations:

1. There has been no accurate knowledge of the level and spread of earnings in the medical and dental professions, nor of how their earnings compared with those of other people of broadly similar attainments.
2. There has been no attempt to ensure that the recommendations of the Spens Committee accepted by the medical profession and the Government as to the spread of earnings among general medical practitioners were carried out.
3. There has been a complete absence of any effective machinery to see that dentists earned what had been intended; as a result they have earned more.
4. Owing to the shortage of dentists, general dental practitioners have worked longer hours and have earned more than was envisaged by the Spens Committee, and more than general medical practitioners.
5. The uniformity of pay scales in the hospital service has not taken account of the wide variation in attractiveness to the young doctors of the various types of hospital.

The commission declares: "We reject the suggestion that doctors' and dentists' pay can be settled by the application of a formula, tied to the cost of living, or to a special index"; and it recommends the setting up of a review body, somewhat similar to the Advisory Committee on the Higher Civil Service, to watch the levels and spread of medical and dental remuneration, and to make recommendations to the Prime Minister.

"The main task of this Body will be the exercise of the faculty of good judgment, and it must be composed of individuals whose standing and reputation will command the confidence of the professions, the Government, and the public. It must be regarded as a better judge than either the Government or the representatives of the professions as to what the levels and spread of medical and dental remuneration should be.

"While the Government cannot abrogate its functions and responsibility for ultimate decisions, we are insistent that the recommendations of the Review Body must only very rarely and for most obviously compelling reasons be rejected."

The commission attaches great importance to prompt action by the Government in dealing with the review body's recommendations. "Nothing will restore confidence between the professions and the Government more than experience of really prompt action on the recommendations of the Review Body."

The commission declares that, now that the vast majority of their earnings come from the State—"a monopoly employer for practical purposes"—doctors and dentists should have their remuneration settled by external comparison, principally, though not necessarily exclusively, with professional men and others with a university background in other walks of life.

In deciding where doctors and dentists should stand in relation to members of other professions, regard should be paid among other matters to the general trend of recruitment in quality and quantity, and to the relative status of the medical and dental professions and of other occupations in other countries. But earnings should not be determined by short-term supply and demand. In common with the Willink Committee, the commission does not propose that attempts be made to alter the level of recruitment by adjusting remuneration.

The report suggests that to supply the review body with the necessary information, the Government must procure a continuous flow of classified statistics showing the level and spread of earnings among doctors and dentists and all who may be regarded as comparable; and this information can most simply and reliably be obtained from the Inland Revenue, with safeguards against identification of individuals or small groups.

As regards dentists the commission views "with disfavour the failure of the profession and of the Government to establish a method that would ensure that dental earnings match intentions.

"Since earnings continue to rise we recommend that no changes in current payments for items of dental service should take place until effective machinery is working to ensure that intentions as to levels of earnings are fulfilled.

"We accordingly recommend that a permanent study group should assess and keep under review rates for items of service based on proved performance of dentists. It will be for the Review Body to say what dentists in the future ought to earn; it will be for the study group to arrange that this is what they do earn."

Doctors and dentists in the public service, the report continues, should not be used as a regulator of the national economy. Their earnings should not be prevented from rising because of a fear that others might follow.

"This does not mean that we consider that either doctors or dentists should ever have a fixed place in a changing world. Over the years, in this country and in others, the financial position held by doctors or dentists may rise in relation to some and fall in relation to others, and in relation to each other, for various reasons including the maintenance of a proper balance of recruitment between these and other professions."

Routine matters of pay adjustments and of general conditions of service should be settled by existing methods of negotiation, whether direct or by a Whitley committee.

The commission gave special consideration to doctors in their preregistration year and first few years of registered practice.

"Today many young science graduates start earning salaries in the early twenties and in many professions earnings are quite substantial well before age thirty. In the light of this, the total earnings of doctors up to age thirty are too low, and we are recommending substantial increases for junior hospital appointments and for trainee assistants; we expect these to

1. Royal Commission on Doctors' and Dentists' Remuneration 1957–60. Cmnd. 939. H.M. Stationery Office. 1960. Pp. 346. 15s.

affect the salaries paid by general medical practitioners to their assistants."

EVIDENCE ABOUT REMUNERATION

The commission quickly realised that to obtain information about earnings in the medical, dental, and other professions it would "have to embark upon a good deal of original research"; and this it painstakingly did.

It has eliminated from all its statistics doctors, dentists, and others (except university teachers) not working full-time. The commission concentrated on those aged 30–65; but it remarks that the figures should be interpreted cautiously, as they are affected by the age structures of the samples. Furthermore, the figures of income returned by general medical and dental practitioners and by fee-earners in other professions included depreciation allowances on capital outlays. (In the case of general medical practitioners these were shown by an expenses inquiry to have averaged £128 in 1955–56, while in the case of general dental practitioners the commission's survey disclosed a figure of £102.) Again, the earnings of general practitioners represent the amounts actually received by them in 1955–56, and take no account of arrears.

In 1955–56 median earnings in all ages (including those under 30 and over 65), and in those aged 30–65, and estimated total earnings at ages 30–65 were as follows:

	Median earnings		*Total earnings*
	All ages *	*Aged 30–65 yr.* *	*30–65 yr.* †
Medical:‡			
General medical practitioners	2058	2160	79,000
Consultants	3100	3130	117,000
Senior hospital medical officers	1822	1850	73,000
General medical service	..	2100	76,000
Hospital doctors	..	2700	100,000
All N.H.S. doctors	..	2300	84,000
Dental:‡			
General dental practitioners	2127	2190	79,000
General dental service	..	2150	78,000
Others:			
Accountants	1350	1490	71,000
Actuaries	1940	2020	105,000
Barristers (England and Wales)	1185	1620	92,000
Advocates (Scotland)	1494	..	72,000
Solicitors (England and Wales)	1750	1850	88,000
Solicitors (Scotland)	1434	1580	67,000
Architects	984	1080	54,000
Surveyors	1146	1360	63,000
Engineers	1181	1210	59,000
University teachers‡	1380	1510	63,000
Graduates in industry	1260	1570	84,000

* No deductions have been made to allow for depreciation, nor, in the case of general medical practitioners, have any additions been made to allow for uneven distribution of pool balances.

† These figures are arrived at by taking the average earnings of each age-group, multiplying them by the number of years in the group (five or ten), and adding them all together. This device greatly diminishes the influence of temporary differences in age distribution, and takes account of the fact that some professions are most remunerative at one age and some at another. The career earnings may be said roughly to represent what a man in each profession who was 30 in 1955 might then reasonably have expected to earn if he worked on a full-time basis until age 65, provided all the circumstances of 1955 remained unchanged.

‡ Men only.

ASSESSMENT OF EVIDENCE

THE commission remarks that the relationship between earnings in different professions is determined not only by considerations of precise justice and logic, but also by tradition and economic pressures of various kinds. Moreover, since increases in professional remuneration are often made at long intervals, in some professions a substantial change may have taken place shortly after the period in which its remuneration was studied. Nevertheless, a broad picture can be seen.

The Willink Committee, reporting in 1957, suggested that "the reduction of the student intake by about a tenth from as early a date as is practicable would meet the case". The commission found that, whether or not as a direct result of the committee's recommendations, the intake of medical students fell from 2564 in 1957–58 to 2504 in the following year. "We are informed that at present all the medical training places can be filled with suitable candidates, but there is no longer the flood of applications that was characteristic of the immediate post-war period. The broad conclusions seem to be that the supply of candidates for training as doctors is reasonably close to requirements, and the question of using remuneration as an instrument either for encouraging a greater flow of potential doctors, or reducing the present flow, does not arise."

As regards dentists, since all available places in the schools are now well occupied, it would be pointless to use remuneration as a means of obtaining more potential dentists. On the other hand: "The level and quality of recruitment to the medical and dental professions may be affected by our recommendations, or the information we publish about the earnings in other professions. Any such changes in the level or quality of recruitment would be matters for consideration when medical or dental remuneration is reviewed in future."

The professions, says the report, in giving evidence to the commission laid great emphasis on what was sometimes called "proper implementation of the Spens Reports".

"We have studied all three reports with great care, but while fully acknowledging the valuable work done by the Committees in providing a basis on which the remuneration of doctors and dentists could at that time be established, we state emphatically that the remuneration of two great professions in the National Health Service can no longer be governed by their recommendations."

The commission acknowledges that its recommendations may lead to repercussions in other fields,

"and that other groups, some paid from public funds, may argue that implementation of our recommendations for doctors and dentists in the National Health Service ought to be accompanied or followed by increases in their own remuneration. . . . it would be quite wrong for us to revise our recommendations for fear of the cost of possible repercussions."

The commission adds that if, after new levels of remuneration are introduced for doctors and dentists in the N.H.S., any other doctors and dentists obtain consequential increases in their remuneration, it would also be quite wrong to use these as arguments for further increasing the remuneration of the N.H.S. doctors and dentists.

The commission reached five main conclusions:

1. At the time of its appointment current earnings of doctors and of dentists were too low.

2. Since 1957 earnings in other professions and in industry and commerce at levels comparable with those of doctors and dentists have increased, by rather less than those of general dental practitioners, but by rather more than those of doctors generally and of dentists in the hospital service.

3. The commission should recommend levels of remuneration to apply from Jan. 1, 1960. Since, however, it was asked to recommend current earnings in 1957 at the time of its appointment, there should be some payment to general medical (but not dental) practitioners and to doctors and dentists in the hospital service to cover the intervening period. There should be no retrospective payment for any period prior to the commission's appointment.

4. Within the medical profession the overall relationship in earnings between the two branches—the hospital service and general practice—should be broadly maintained unchanged.

5. The young doctor under 30 years of age has been underpaid to a relatively greater extent than older doctors, but the young dentist has not been underpaid in relation to the older dentist.

"After careful consideration of all the factors we have decided that in 1957 average earnings of both doctors and

dentists for the whole career period between ages 30 and 65 should have been about £7000 more than they actually were in 1955/56, and that by 1st January 1960 they should have increased by a further 12 per cent. This would give average 'career earnings' from January 1960 of about £102,000 for the National Health Service doctor and of about £96,000 for general dental practitioners. We have also decided that as from 1st January 1960 the younger doctors should receive rather higher percentage increases."

HOSPITAL AND SPECIALIST SERVICES

The suggested new scales of salaries are set out in the accompanying table.

Consultants

The commission recommends that as from Jan. 1, 1960, the scale for whole-time consultants should be: £2550 at age 34 or on appointment later × £150 (8)–£3750; then after a second year at £3750 one further increment of £150–£3900. The commission has lengthened the scale slightly in order that consultants can look forward to increasing remuneration for a rather longer period than in the past.

The commission is not persuaded by the arguments in favour of weighting; but it admits that its immediate abolition would alter the relativities between whole-time and part-time consultants more than seems justified at present. It therefore recommends retention of a limited amount of weighting on the remuneration of part-time consultants in post on Dec. 31, 1959, and on that of certain others.

No change is recommended in the circumstances in which payment is made for domiciliary visits.

Of distinction awards the commission says:

"For our part, we agree that some considerable differentiation of income among consultants is necessary in order that good work may be encouraged and rewarded and that there may be a spread of income among consultants comparable to that in other professions. Two common methods of securing differentiation in other fields are not open to the consultant so far as his Health Service work is concerned. Unlike some professional men in private practice he cannot vary his fees in accordance with his professional standing; and unlike the salaried employee in most fields he cannot look forward to promotion. In these circumstances we consider the awards system is a practical and imaginative way of securing a reasonable differentiation of income and providing relatively high

PAST, CURRENT, AND RECOMMENDED SCALES

Grade (1)	Scales payable when Royal Commission was appointed. (2)	Current scales (i.e., column (2) plus two interim increases) (3)	Scales proposed by British Medical Association "in 1957 figures" (4)	Recommended scales as from Jan. 1, 1960 (5)
Consultants (*a*) Basic scale	£1800 at age 30 or less. £1950 at age 31. £2100 at age 32 or over × £125 (8)–£3100.	£1965 12*s.* at age 30 or less. £2129 8*s.* at age 31. £2293 4*s.* at age 32 or over × £136 10*s.* (8)–£3385 4*s.*	At age 32 the scale to be £2700 × £162 10*s.* (8)–£4000.*	£2550 at age 34 or on appointment later × £150 (8)–£3750; then after a second year at £3750 one further increment of £150–£3900.
(*b*) Distinction awards	A awards—£2500 (to 4% of all consultants). B awards—£1500 (to 10% of all consultants). C awards—£500 (to 20% of all consultants). (The basic scale of consultants with A and B awards is abated by £300 and £200 respectively.)	As in column (2)	A awards—£4000 (to 4% of all consultants). B awards—£2400 (to 10% of all consultants). C awards £800 (to 20% of all consultants).	100 A Plus awards of £4000. 300 A awards of £3000. 800 B awards of £1750. 1600 C awards of £750.
Senior hospital medical and dental officers	£1475 at age 30 or less. £1525 at age 31. £1575 at age 32 or over × £50 (9)–£2025	£1610 14*s.* at age 30 or less. £1665 6*s.* at age 31. £1719 18*s.* at age 32 or over × £54 12*s.* (9)–£2211 6*s.*	At age 32 the scale to be £2160 × £130 (8)–£3200.	£2000 at age 34 or on appointment later × £75 (4)–£2300; thereafter increments of £100 every second year–£2700.
Senior registrars ..	£1100 in the first year. £1200 in the second year. £1300 in the third year. £1400 in the fourth and any subsequent years.	£1258 8*s.* in the first year. £1372 16*s.* in the second year. £1487 4*s.* in the third year. £1601 12*s.* in the fourth and any subsequent years.	£1620 in the first year. £1800 in the second year. £1980 in the third year. £2160 in the fourth year. Further increments of £180 per annum to be given for any further years in the grade while awaiting consultant posts.	£1500 in the first year. £1600 in the second year. £1700 in the third year. £1800 in the fourth year. £1900 in the fifth year. £1900 in the sixth year. £2000 in the seventh year. £2000 in the eighth year. £2100 in the ninth and any subsequent years.
Registrars	£850 in the first year. £965 in the second and any subsequent years.	£972 8*s.* in the first year. £1103 19*s.* in the second and any subsequent years.	£1260 in the first year. £1440 in the second year. Further annual increments of £180 for each additional year in the grade.	£1250 in the first year. £1400 in the second and any subsequent years.
Junior hospital medical officers	£775 × £50 (6)–£1075.	£886 12*s.* × £57 4*s.* (6)–£1229 16*s.*	£1100 × £100 (5)–£1600.	£1100 × £60 (8)–£1580.
Senior house-officers ..	£745	£852 6*s.*	£1080	£1050 on appointment at age 27 or under. £1100 on appointment at age 28 or over.
House-officers	£425 per annum for first pre-registration post held. £475 per annum for second and any subsequent pre-registration post held. £525 per annum for any post held when fully registered.	£486 4*s.* per annum for first pre-registration post held. £543 8*s.* per annum for second and any subsequent pre-registration post held. £600 12*s.* per annum for any post held when fully registered.	Preregistered: £555 per annum. Fully registered: £635 for first post held. £715 for second post held.	£675 per annum for first post held. £750 per annum for second post held. £825 per annum for third and subsequent posts.

*The British Medical Association also proposed: Weighting for part-time service should be re-established at pre-1954 levels. Consultants appointed after age 32 should be placed on the scale according to age and experience. Domiciliary consultation fees should be increased by 60%. The obligation on the whole-time consultant to perform eight consultations per quarter without fee should be abolished.

earnings for the 'significant minority' to which the Spens Committee referred. We therefore unreservedly support the continuation of the system."

It adds that at some time in the future selection for C awards might be made regionally.

The commission finds nothing surprising in the different proportions of consultants in different specialties who hold distinction awards. "Some specialties require more extensive training and experience and involve more difficult techniques and a heavier responsibility than others." On the other hand the commission is not satisfied that the number of awards should always be decided on the basis of percentages of all consultants; and it recommends that for the years 1960–62 awards (on a whole-time basis) be made as follows: 100 A-plus awards of £4000; 300 A awards of £3000; 800 B awards of £1750; and 1600 C awards of £750.

Senior Hospital Medical Officers

These, says the report have reached the maximum too soon, and this maximum has been too low in relation to other grades. The commission recommends as from Jan. 1, 1960, the following scale: £2000 at age 34 or on appointment later ×£75 (4)–£2300; thereafter increments of £100 every second year–£2700.

House-officers

"We consider," says the commission, "that house officers have been greatly underpaid both in relation to their seniors and in relation to what is paid to comparable people in other professions." It recommends a salary of £675 per annum in the first post, of £750 in the second post, and £825 in the third and subsequent posts.

Senior Administrative Medical Officers

The maximum of the scale of remuneration paid to senior administrative medical officers in the largest regions should, as until recently, be the same as that of a full-time consultant, with a C award; and the whole scale should consequently be recast.

GENERAL PRACTICE

The Pool

In the commission's view, the pool system of remuneration, though unusual, has a number of practical advantages, and recommends a continuance of the system, but not in precisely its present form.

"It has been suggested to us by Government witnesses that the pool should be calculated by reference to the number of users of the service rather than of the doctors providing it. The main objection to such a change is that it would not be possible, as it is under the present system, to decide upon a level of earnings for the average doctor and be sure of achieving it. If the pool were based on the number of patients and not on the number of doctors there would be a tendency, in current conditions, for remuneration to fall, since the population is not increasing as fast as the number of doctors. In order to restore the intended level of earnings it would then be necessary to make successive increases in the rate of capitation and other fees. No worthwhile public economies would be likely, but doctors' incomes would fluctuate more, which is not a desirable feature in a system of remuneration . . . We therefore recommend that no change be made in this matter, and that the pool continue to be calculated by reference to the number of doctors."

"On the other hand we consider that the balance of advantage lies in the removal from the annual pool calculations of private earnings (from private patients, examinations for insurance companies, part-time industrial practice, and other private sources). Private earnings are . . . very difficult to ascertain on an exact or agreed basis, and it is for this reason that we recommend that the present unsubstantiated figure of £2 million be dropped from the annual pool calculations, and that no attempt be made in future to calculate and allow for annual fluctuations unless there is reason to believe that the alteration has been substantial."

Exchequer contribution to superannuation should no longer be deducted in arriving at the sum payable to doctors. The reasons for its inclusion hitherto in the pool have now lost their force.

Special inducement payments made to practitioners in certain sparsely populated areas should be taken into account as income from the National Health Service in making up and distributing the pool.

The pool should be based on a predetermined average net income from all official sources (excluding the differential payments referred to below); this should be multiplied by the number of unrestricted doctors under 70 in the service; there should be added an annually estimated total figure of practice expenses and subtracted an annually ascertained figure of earnings from hospitals, local authorities and official sources outside the National Health Service.

Recommended Levels and Distribution

As from Jan. 1, 1960 there should be paid into the pool the sum of £2425 per annum in respect of every practitioner below the age of 70 providing unrestricted general medical services. No change is recommended in the general system of allowing for practice expenses.

No detailed scheme is suggested for the distribution of the pool, but the report adds the following comments:

"First, while we entirely approve of the efforts that have been made, and successfully made, to encourage the formation of partnerships, we feel that the financial incentive at present provided is somewhat excessive. . . . Secondly, while we fully approve the policy of giving to the rural practitioner some financial recompense for the facts that he cannot, in a scattered practice, attend so many patients as he could if they lived closer together, and that his expenses in attending them will be proportionately greater, our figures reveal that here again, in England and Wales at any rate, a sound measure has been overdone. We accordingly hope that in the scheme of distribution to be worked out the special benefits at present given at the expense of other practitioners to partners and to rural and semi-urban practitioners, while not abandoned, may be relatively somewhat reduced. Thirdly, in order to mitigate to some extent the preponderant influence of list size as a determinant of earnings, we hope that, where practicable, greater weight will be given in the scheme of distribution to items other than capitation. Fourthly, we trust that the system of initial practice allowances, subject to any appropriate adjustments in amount, will continue to be operated for the elimination of under-doctored areas.

"Finally, we regard it as important that the distribution of the pool balance should be made more promptly, and that the amount left to be distributed in this way should be greatly diminished."

It had been suggested that the financial recommendations should be linked to a proposal to reduce the maximum permitted list of patients, but the commission are convinced that this is not a question they are competent to settle, and indeed, such is the variation in human capacity and local circumstance, that they doubt whether anyone is competent to set a fixed and universal limit to the number of patients a doctor should have. The absolute maximum must clearly be above the number that it is thought an average practitioner can handle in average circumstances. If the maximum should be reduced the revised scheme of distribution that will then have to be made should be so

devised as to reduce as little as possible the already inadequate spread of incomes, and as not to cause a substantial reduction in the earnings of individual practitioners already established. In any revision of the regulations regarding list size, care should also be taken not to render it impossible for a practitioner who employs an assistant to find the money to pay him adequately.

General-practitioner Differential Payments Scheme

Over and above the finance needed to meet other recommendations, a special fund of £500,000 per annum should be provided expressly to recognise distinguished general practice by additional remuneration. While leaving the details of such a scheme to be worked out by the profession and the Government, the commission suggest the following:

(*a*) The additional remuneration of a selected general practitioner should be not less than £500 per annum and might well amount to £1000 or even more.

(*b*) Those selected for the additional remuneration should normally continue to enjoy it until retirement.

(*c*) The addition should be treated in all respects as part of the practitioner's National Health Service remuneration.

Assistants

Trainee assistants are paid (indirectly) by the State and it is recommended that for the sum of £775 that was prescribed in 1955–56 there should be substituted as from Jan. 1, 1960, the sum of £1150 with such adjustment of the car allowance as may be deemed fair. For other assistants the position is not so simple, since their payment and conditions of service are governed by individual contracts with their principals, and the report does not recommend a standard or indeed a minimum rate. "We trust, however, that the remuneration of assistants will in fact rise in keeping with that of all other young doctors."

Dissenting Report

Prof. JOHN JEWKES, in a memorandum of dissent, says: ". . . . in my opinion, the recommendations of my colleagues in regard to the level of earnings of general practitioners and of part-time consultants will not suffice to restore confidence in these two vital sections of the profession, nor will they provide in the long run an adequate supply of doctors of quality to meet the needs of the service and any improvements that may be sought in it."

Professor Jewkes' recommendations include the following:

1. That the annual earnings of general medical practitioners in the N.H.S. should be based, as from Jan. 1, 1960, on an average net figure (excluding private earnings and the Exchequer superannuation contributions) of £2550, and not on a figure of £2425 as recommended in the report.

2. That no change should be made in the weighting applied to the earnings of part-time consultants or senior hospital medical officers.

3. That no change should be made in the system of distinction awards except that the value of each class of award should be increased by 30%.

4. That fees paid to consultants for domiciliary visits should be increased by 30%, and whole-time consultants should be paid for all such visits.

5. That no retrospective payments should be made to general medical practitioners or to hospital staff.

6. That the new machinery for reviewing remuneration should take the form of an advisory council with somewhat wider functions than those suggested in the report. The council should review remuneration every three years, or sooner if the price level has changed either way by more than 10% from the time of the last settlement.

In England Now

A Running Commentary by Peripatetic Correspondents

WE lament the passing of Charlie. Our part of Lambeth, with its decaying early Georgian dignity, boasts a shopping centre of course, but one which adheres pretty strictly to the Shop Hours Act of 19-whatever-it-was, and if one gets a bit delayed in the Tube not a loaf of bread nor book of verse can one buy. Flasks of wine, obviously, can be purchased at a number of off-licences until 8.30 P.M. and after. Which is why we lament the passing of Charlie. His little shop up our road had a timeless quality. Generations of feet had worn its single step, and though it was scarcely larger than a phone-box Charlie packed into it an infinite number of useful objects from socks via stewing steak to gob-stoppers. He invariably had some kind of remedy for a depleted larder, and his light shone forth until after 9 P.M. "Knock me up if the door's locked," he offered cheerily. "Can't have folk going hungry." At times of particular difficulty, such as a late return on Bank Holiday Monday when the diminutive shelves had long been stripped of comestibles, he has been known to slip back into his cosy little room at the rear and emerge with a lump cut off the end of his own loaf. "Here," he whispered, "have half of mine—tide you over till morning," and then refuse payment. His industry and keen business sense paid off, and as the boutique could not take more than two customers (and then only at some inconvenience and hazard to the precarious boxes of bullseyes) an unruly conclave was to be witnessed in the road from half-past a fine five o'clock as scruffy kids bearing a few pence jostled with returning artisans and hurried housewives to gain entrance to the sanctum.

Yes, we lament the passing of Charlie. Time, woodworm, and rot had taken their toll of Charlie's aged terrace, and the demands of a nearby school for more playgrounds persuaded our Council some 13 years ago to condemn the lot. Lightheartedly we thought we were secure in the Law's delays, but shortly before Christmas the bulldozers moved in. Still shone the light forth, however, and though Charlie no longer troubled to stock up, business was as usual as the dust blew around him and we expected him to go down with his little shop, standing as it were upon the bridge. It was not to be: Charlie went, but with a whimper, not a bang. We glanced over to the usual place, and suddenly saw only the faded cigarette advertisements and a padlocked door. Charlie had folded his tents and crept silently away—and very nicely judged, too, we gather, because the Council had set him up in a much larger establishment three miles away just in time for the Christmas rush. Well, may he prosper; but we shall not see him again. To us his ghost lingers over the spot where asphalt will be laid and where children will soon play marbles and suck bullseyes.

* * *

A professor we know is not very good at answering letters, so a month or two ago we sent him a Mallaig kipper in a plain envelope. Yesterday we made a quick inspection of the correspondence compost heap on his enormous desk. The kipper has not yet surfaced, though our olfactory organs noted that its presence is becoming perceptible. But this is clearly the wrong approach. We should have remembered Sherrington's teaching that the sense of smell—"rich in affective tone"—quickly adapts and loses interest after the first encounter.

Now we have hit on a better plan. A firm of paper-makers has obligingly prepared for us, by a secret process, some special notepaper guaranteed to ignite spontaneously after 4–6 weeks. We are awaiting the result of this experiment with interest and hope that *The Lancet*, having accepted this preliminary communication, will be prepared to publish our full report in due course.

We expect, at least, to earn the gratitude of the professor by clearing his desk of unopened advertisements for Totamicin.

* * *

Last month I sat the examination for the membership of the Institute of Advanced Practitioners (M.I.A.P.). It is conducted by retired Civil Servants from the Ministry of Health. The practical tests vary according to the type of practice. The urban practitioner, for instance, may be given a number of passport photos to compare with standard subjects in a given time and make the appropriate comment on the backs; the rural doctor on the other hand may be given a bundle of E.C.10s to sort into packets of a hundred or a given number of old ointment jars to wash out in a specified time. Two of the questions from my written paper were:

(1) Write brief reasons for any two of the following—Med. 2a; OSCI; FW 8; BM 4(Rev); DMO.

(2) The Ministry decides that seamless fine-thread two-way-stretch thigh-length hose shall no longer be prescribable. Discuss an alternative treatment for chilblains.

In my viva I was asked to give the percentage of the shillings collected on prescriptions which I allocated to my wife's pension fund, to dictate a letter to the National Assistance Board for a grant towards extra coal for a patient's television viewing-room, and to name the last five Ministers of Health in the correct order.

I passed, paid my first annual subscription of 18*s*., and can now display a neat red-tape bow on the chest-piece of my stethoscope and the Institute's badge on my car. This depicts a graduate in tattered academic dress discreetly manacled to an executive council clerk whose neat suit is unmistakably Savile Row.

* * *

As a peripatetic psychiatrist I recently visited an Ayurvedic mental health research department, supervised by a scholarly Brahmin who is a pandit of the Vedic texts. His assistant demonstrated the patients under their care, and his sweeping therapeutic optimism disarmed my dubiety about the potions, and the glutinous pastes for external application to the head, which were his principal medicaments. At least the principle of *primum non nocere* seemed to be observed, and in psychiatry that is something.

The pandit himself obliged with a brief outline of Vedic teachings on abnormal psychology. On being asked whether he had difficulty in communicating with his Western-trained colleagues, he explained that he was even now studying Dr. Curran's introductory textbook. With a beatific smile, he pointed to the heavens and said: "God bless him for his simple lucid explanations!" I have never heard any textbook receive such a heartfelt recommendation.

* * *

DEPRECIATION

Look—there's plenty to do when you're thirty
Though the shadows are gathering fast.
You may think that we old 'uns have had it,
You may think that we live in the past;
But old age makes a fellow more willing
And he'll work, just as long as he'll last.

Now the way to survive when you're thirty
Is to plan for it, right from the first.
You must Live while you're young—but not *too* much—
To get rid of Youth's feverish thirst,
And then stock up your mind for retirement;
It's the thoughtless ones feel it the worst.

You don't squander yourself, when you're thirty—
You must always make sure of your sleep.
Lord! The way you see some of 'em living
It's enough for the angels to weep;
But with care you can keep up your walking—
In the parks, where the hills aren't too steep.

It's important to plan, when you're thirty;
You must *spread* yourself over your week
And you mustn't pay too much attention
If you notice your vertebræ creak;
And if ever you're hustled by youngsters—
Just you turn a deaf ear to their cheek!

Letters to the Editor

MEDICAL NEEDS OF INDIA

SIR,—I was glad to read your editorial of Jan. 30 in which you draw attention to the vast problem of India's medical needs.

As one whose professional career for 31 years has been spent almost entirely in North India, I should like to endorse much of what you say, and also to emphasise the need of help from outside India. In this connection I think two statements in your article may give a wrong impression, and thus tend to discourage any who might feel disposed to offer to serve in India.

"Though some of the missionary hospitals and schools were outstandingly good and these continue—for example, Vellore, which has plenty of candidates for its medical school—the Government does not look with favour on missionary effort." It is true that the Government of India does not encourage the initiation of entirely new ventures, but I know of no restrictions placed on existing medical missionary work, and no interference with the running of medical institutions. While there may be the occasional unfriendly official, the policy of the Central Government seems rather to encourage mission hospitals, many of which receive financial assistance, recurring or otherwise.

The following figures taken from the latest edition of *The Christian Handbook of India*, give some idea of the present strength of mission hospitals run by Protestant bodies:

Total no. of hospitals	238
This includes:	
Those of over 50 beds	60
" " " 100 "	55
" " " 150 "	14
" " " 200 "	7
" " " 350 "	4

There are many smaller units, and all have comparatively large outpatient departments.

In addition there are 11 tuberculosis sanatoria and 52 leprosy institutions.

Many of the larger hospitals are training nurses and are recognised by the Government for this purpose. The nurses take the examinations of the local provincial Government.

There are numerous dispensaries and some hospitals at work in village districts—that "backward countryside" where, as you rightly point out, the need is greatest.

I was once personally assured by a Government official of some importance that the type of work being done by these small medical mission units is what is needed, and is commendable in his opinion.

Your second statement, that "even medical missionaries are being slowly eliminated as replacements fall due, fewer being allowed to enter than to leave," does not accord with the facts.

In its policy relative to the entry of foreigners into India the Government has shown no discrimination against medical missionaries, and no difficulties are placed in the way of those returning to their mission posts from leave in Great Britain.

The admission of non-Commonwealth persons is subject to certain restrictions, however, but these apply equally to all, whether medical or non-medical, missionary or otherwise.

It is true that the total number of medical missionaries is smaller than some years back, but this is largely due to a lack of new volunteers. Another cause is the deliberate policy of mission hospitals in appointing Indians to posts of responsibility wherever possible, but this is an entirely voluntary matter.

The door of opportunity for medical service in India is still open, especially to those with a missionary vocation.

E. JOYCE ROBINSON
Bible Churchmen's Missionary Society,
Kachwa,
District Mirzapur,
Uttar Pradesh,
India.

Lowestoft.

SAFETY-HARNESSES IN CARS

SIR,—We have read with interest Mr. Barrett's article of Feb. 6 on the early treatment of stove-in chest. We notice that he does not mention the importance of safety-harness in cars, which in our opinion would have been a major factor in the prevention of these injuries. Mr. Barrett states that " death steps in . . . unnecessarily ". We agree: most of these deaths could have been prevented.

The commonest cause of these accidents is the driver or passenger being thrown forwards on to the steering-wheel or dashboard. This forward movement, which often includes the seat, could be prevented by a well-designed pelvic or pelvic-shoulder harness which is bolted to the floor with a reinforced steel plate some distance behind the front seat. This harness must be fitted with nylon webbing capable of withstanding a strain of several thousand pounds.

In addition, we should like to point out that in a detailed analysis of road accidents, over 30% of passengers are thrown out of the car at the moment of impact because the doors of the car spring open. These injuries, too, would be prevented by adequate pelvic or pelvic-shoulder harness.

It is, however, important that such harnesses be constructed of strong material, well designed, and securely bolted to the floor. Cheap materials, shoddy buckles, and belts which are looped around the back of the seat are utterly useless.

G. P. ARDEN
D. M. WALLACE.

London, W.8.

THE THORN IN THE FLESH

SIR,—Following Dr. Buhr's article (Feb. 6), this case-report shows that a generalised allergic response may follow injury by the thorn of the blackthorn.

A housewife, aged 61, was admitted to Southmead Hospital on Sept. 24, 1959, with the history that, while blackberrying three days previously, she had scratched her arm on a blackthorn bush (she was emphatic that it was blackthorn rather than blackberry). A few hours later she developed an irritating rash at the site of the scratch, which spread within a few hours to involve the whole arm, and then the rest of her body; at the same time she became increasingly short of breath. She was previously in good health, and there was no personal or family history of allergic disease or asthma.

On admission she was dyspnœic at rest, with a respiratory-rate of 46, and slightly cyanosed. Her temperature was 100°F. Her whole body was covered in a vesicular rash, secondarily infected in places. Examination of her chest showed pronounced expiratory effort, supraclavicular recession, generalised bronchospasm, and occasional, scattered rales.

Investigations showed a white-cell count of 14,400 per c.mm. (8% eosinophils, absolute eosinophil count 1150). Chest X-ray was normal.

Her bronchospasm and urticaria settled only slowly with ' Franol ' (ephedrine, phenobarbitone, and theophylline) and chlorpheniramine, and she was fit for convalescence only after 18 days' inpatient treatment.

I am grateful to Dr. Francis Page for permission to publish details of this case, which was under his care.

Southmead Hospital,
Westbury-on-Trym, Bristol. B. A. LATHAM.

SIR,—Dr. Buhr's article was most interesting, for blackthorn injuries are by no means uncommon in agricultural districts and prompt me to record this case.

A schoolboy, aged 9, was seen in the casualty department of High Wycombe Hospital on June 20 last year. He had fallen, injuring his left elbow, and had tenderness at the lower end of the humerus, with a full range of movement. There was no skin wound and X-ray revealed no bony injury. He was treated with a collar-and-cuff sling, and by June 30 was completely symptom-free.

On Oct. 16 he returned complaining of a lump in the left arm. There was a small mobile mass over the postero-medial aspect of the left humerus which was apparently in the triceps muscle. This mass was tender and thought to be an encysted hæmatoma resulting from the injury in June. No immediate treatment was advised. By Nov. 13 the tumour was slightly larger and still tender and mobile. Excision was advised, and on Nov. 24, 1959, with a bloodless field, the lump was explored and proved to be a mass of fibrosis (approximately $^3/_4 \times ^3/_4 \times ^1/_2$ in.) in the triceps muscle. The specimen was cut open at the end of the operation and a $^1/_4$-in. tip of a blackthorn was revealed. The wound healed satisfactorily, and when last seen the patient had no disability.

Section of the specimen showed " fat necrosis and granulation tissue containing some brown pigment suggestive of old hæmorrhage and a number of areas of foreign-body reaction ".

This case is interesting in that there was no skin wound and nothing to show the entry of a foreign body. It illustrates a profuse foreign-body reaction which was stimulated by blackthorn.

I am grateful to Mr. G. J. Walley for permission to record and treat this case.

The General Hospital,
Burton-on-Trent. P. C. CASHMORE.

TREATMENT OF INGUINAL HERNIAE

SIR,—I think Mr. Moloney (Feb. 6) is undoubtedly right in stressing the extra care that is taken with recurrent herniæ. In considering this problem of herniorrhaphy it is pertinent to recall that most recurrences after indirect herniæ are indirect herniæ again, and although we may be certain we have removed the sac high enough at the first operation, when the recurrence appears well within the first twelve months we might well ask ourselves where has this new sac come from?

Consideration of this over the last three years has led me to look for, and often find, lax peritoneum on the medial side of the neck of the sac which can be drawn out by hooking the medial half of the neck over the first joint of the index finger. In this way the peritoneum can be rendered as tense on the medial side as it is naturally on the lateral side. In this way I find I am removing more sac than I had done previously.

The second problem in the initial repair of herniæ is the securing of absence of tension on the repair particularly in the lateral part of the posterior wall, and if the absence of tension is being secured by release of the ligament from the fascia lata, from below rather than from above (Tanner slide), then simple pressure upwards with the finger after the repair is completed at the site of the internal abdominal ring will determine whether or not the ligament is being pulled down by any residual attachment of the fascia lata to it laterally.

If the impression is that there is still tension from below then it is necessary to further release the fascia lata laterally from its attachment to the fibres of the external oblique at its lower border. Confirmation of absence of tension using this method of repair can be gained if the patient is made to cough during the anæsthetic at the end of the operation when free movement of the lower border of the external oblique upwards will be seen to occur if there is no pull from below.

This principle of absence of tension applies equally to any form of repair or reconstruction, including a nylon " darn ". It particularly applies if the mobilised ligament is being sutured up to the conjoint tendon, after release from the fascia lata.

The Memorial Hospital,
Peterborough. D. W. BRACEY.

HIGH PLASMA-IRON IN PORPHYRIA

SIR,—Dr. Hathorn and Dr. Lamont (Jan. 30) refer to high values of plasma-iron found in cases of porphyria (? acute intermittent porphyria) in Africans, and ask if plasma-iron has been measured "in cases with other types of porphyria".

In my translation of Vannotti's book,[1] it is stated that in acute intermittent porphyria a fairly regular increase in serum-iron has been found,[2] values ranging from 120 to 220 μg. per 100 ml., and also iron deposition in the organs. In his recent survey, Goldberg [3] found that the hæmoglobin in 27 cases of this disease lay within normal limits.

The extensive deposition of iron in the organs of the congenital porphyria patient, Petry, is well known from the classic investigation of Borst and Königsdörffer.[4] Two forms of iron-containing deposit were observed, hæmosiderin and a form in which iron was associated with a brown, amorphous pigment. Quantitative serum-iron analyses are not available.

In a case of cutaneous porphyria with easily traumatised skin and formation of bullæ, Langhof and Mildschlag [5] reported very high serum-iron values.

Whilst it is difficult to interpret these findings with certainty, it is clear that iron metabolism may show signs of abnormality in the various porphyria diseases. The role of iron in normal porphyrin [6] and hæm [7] formation is being very actively investigated at the present time in several different laboratories.

Department of Chemical Pathology,
University College Hospital
Medical School,
London, W.C.1. C. RIMINGTON.

URINARY EXCRETION OF PORPHOBILINOGEN IN ACUTE PORPHYRIA

SIR,—It is well known that acute intermittent porphyria is more common in females than in males. It is also known that in patients with acute porphyria attacks are provoked by endocrine imbalance. Durst and Krembs [8] and Hughes [9] described instances of attacks during pregnancy and the puerperium. Levit et al.[10] recorded a case of acute porphyria with premenstrual attacks and exacerbations caused by progesterone injections. More than a year ago we also observed two attacks in connection with endocrine dysfunction in a 46-year-old woman suffering from acute porphyria. This presumably climacteric patient had had two periods of amenorrhœa, each lasting about six months and ending in menstrual bleedings and attacks of porphyria.[11] With the determination of the daily output of the porphyrin precursor, porphobilinogen (P.B.G.), in the urine, it was possible to demonstrate in this patient some relation between porphyrin metabolism and endocrine imbalance.

We followed this patient for three months, beginning about nine months after her second attack, and we determined the daily P.B.G. output in the urine by the method of Mauzerall et al.[12] slightly modified. The accompanying figure shows the daily P.B.G. levels in the urine.

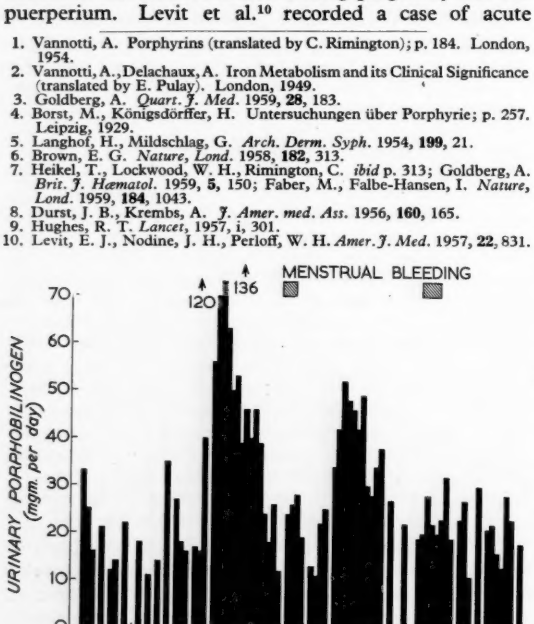
In the first weeks of observation the patient had no menstrual bleedings (her last bleeding was in March, 1959) and no high urinary P.B.G. levels either. However, 14 to 16 days before her first (July 3–5, 1959) and second (Aug. 2–5) bleeding there was an increase in the urinary P.B.G. level. Thus the period of high urinary P.B.G. output coincided with ovulation. During high urinary P.B.G. excretion her clinical state deteriorated slightly, especially before her first bleeding.

During our observation period a third bleeding has not been reported and she is again amenorrhœic. Urinary P.B.G. levels are not high.

Our observations show that in this patient 14 to 16 days before bleeding after a period of amenorrhœa the P.B.G. excretion in the urine increased. This increase coincided with the time of ovulation. The increased urinary P.B.G. levels before the patient's first bleeding were similar to those observed during her attacks (140–165 mg. per day). We suppose, therefore, that in this case endocrine imbalance plays an important role in precipitating attacks of porphyria.

G. KELÉNYI
GABRIELLE ARATÓ
V. BUDA
S. ORBÁN.

Department of Pathology,
Medical University of Pécs, and
Municipal Hospital of Kaposvár,
Hungary.



Daily porphobilinogen levels in urine.

AUTOIMMUNE HÆMOLYTIC ANÆMIA WITH RENAL FAILURE DUE TO PHENACETIN AND P.A.S.

SIR,—Your issue of Jan. 2 contained an article on this subject by Dr. MacGibbon and her colleagues. Because of the rarity of such cases I should like to report another case [13] of a hæmolytic reaction due to *p*-aminosalicylic acid (P.A.S.).

A 57-year-old man suffered from pulmonary tuberculosis for several years. He had been treated with different antibiotics and with P.A.S. Oral P.A.S. was badly tolerated (vomiting, general malaise, and fever). It was therefore decided to give a P.A.S. solution intravenously (15 g. daily) with 250 mg. of oxytetracycline. His clinical condition improved, but at the beginning of the 10th infusion of P.A.S. he had a violent reaction (lumbar pain, rigors, vomiting, and collapse), and the infusion was immediately stopped. He became very anæmic, the hæmoglobin fell to 48%, the serum-bilirubin increased, and the red cells showed anisocytosis and spherocytosis. After three days, when the patient was already recovering, we received the blood for serological investigations:

Blood-group B_{a_1}, Rh-negative; direct Coombs test negative.

Besides incomplete Rh antibodies anti-D, apparently the result of transfusions with Rh-positive blood, the serum contained a second antibody. This antibody agglutinated the cells of the patient and other Rh-negative subjects, but only in the presence of P.A.S.

1. Vannotti, A. Porphyrins (translated by C. Rimington); p. 184. London, 1954.
2. Vannotti, A., Delachaux, A. Iron Metabolism and its Clinical Significance (translated by E. Pulay). London, 1949.
3. Goldberg, A. *Quart. J. Med.* 1959, **28**, 183.
4. Borst, M., Königsdörffer, H. Untersuchungen über Porphyrie; p. 257. Leipzig, 1929.
5. Langhof, H., Mildschlag, G. *Arch. Derm. Syph.* 1954, **199**, 21.
6. Brown, E. G. *Nature, Lond.* 1958, **182**, 313.
7. Heikel, T., Lockwood, W. H., Rimington, C. *ibid* p. 313; Goldberg, A. *Brit. J. Hæmatol.* 1959, **5**, 150; Faber, M., Falbe-Hansen, I. *Nature, Lond.* 1959, **184**, 1043.
8. Durst, J. B., Krembs, A. *J. Amer. med. Ass.* 1956, **160**, 165.
9. Hughes, R. T. *Lancet*, 1957, i, 301.
10. Levit, E. J., Nodine, J. H., Perloff, W. H. *Amer. J. Med.* 1957, **22**, 831.
11. Kelényi, G., Arató, G., Buda, V. *Orv. Hetil.*, 1959, **100**, 186.
12. Mauzerall, D., Granick, S. *J. biol. Chem.* 1956, **219**, 435.
13. van Loghem, J. J., Jr. 3rd International Congress of Clinical Pathology. Brussels, July, 1957.

No agglutination could be obtained when the other drugs which the patient had received (oxytetracycline, isoniazid, penicillin) were added to the patient's serum. In the maximal concentration of P.A.S. (500 mg. per 100 ml.) optimal reactions were obtained (titre 32). As the concentration of P.A.S. diminished the titre fell gradually. The antibody was still active after heating at 56°C for 20 minutes, but was destroyed by heating at 70°C for 10 minutes.

Hæmolysis could not be demonstrated with fresh serum samples, nor with inactivated serum samples to which human or guineapig serum had been added as a source of complement. The antibody in the patient's serum was not neutralised by the addition of P.A.S. solution to the serum, nor could it be removed by adsorption on to packed cells, but it was completely removed after the addition of P.A.S. + red cells.

It seems well established that the antibody developed in the course of the treatment by intravenous injection of P.A.S., because repeated oral administration of P.A.S. was never followed by signs of abnormal cell destruction, and also because the antibody disappeared a few weeks after the intravenous P.A.S. was stopped.

Another case of autoimmune hæmolytic anæmia induced by P.A.S., this time by oral treatment, was recently observed by Dr. J. Dausset in Paris (unpublished observations).

Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam. J. J. VAN LOGHEM, Jr.

SIZE DIFFERENCES AND SOCIAL CLASS

SIR,—In your editorial of Feb. 6 on the Germ-free Animal you say that the difference in size between adolescent boys in social class I and those in social class V is no longer seen. I believe this statement to be in error, as reference to the texts on growth [1] or to the original literature [2] will readily show. On the contrary, the most striking thing about the changes in growth-rate which have occurred in the past fifty years is that *all* social classes are growing up earlier and that the difference between the classes, though it may have decreased a little, has not decreased as much as many of us would expect. One is reminded of the parallel situation in infant mortality described recently by Professor Morris and his colleagues in your pages. The reasons for the social class differences in growth-rate and in final adult size are evidently not simple, and the subject invites much more careful research.

Institute of Child Health, London, W.C.1. J. M. TANNER.

PRESERVATION OF MEDICAL RECORDS

SIR,—Your article (Feb. 13, p. 379) drawing attention to the British Records Association memorandum on the disposal of medical records is welcome. The historian and archivist have a legitimate interest in medical records which should be as far as possible respected.

Medical records are more than archives, however, and for half a century or so may help to preserve the lives and limbs of those to whom they refer, if they are intelligible and accessible. The growth of procedures in modern medicine is reflected in increasingly complex medical records. In this hospital the mean number of sheets recording a single admission was 9·3 in 1946, 12·6 in 1952, and 18·9 in 1956, although the mean duration of admission fell slightly during that time. If the information thus recorded is to play its full part in exhibiting all features of an illness to those caring for the patient, either then or later, the record must be more than a sheaf of papers arranged at hazard.

The increasing bulk of medical records makes microfilming a likely solution to the problem of storage; microfilming is most effectively applied to a record system designed for it, precautions being taken to preserve documents in a physical state that permits microfilming without laborious preliminary treatment.

With these two requirements of medical records in mind we have designed a system of clinical records which has been in operation at the United Cardiff Hospitals since April, 1958; it is proposed that microfilming of the new records will begin when they are 5 years old.

A. H. JAMES
Cardiff Royal Infirmary. JOHN MORGAN.

POSTOPERATIVE DIARRHŒA

SIR,—A further point must be made concerning postoperative diarrhœa and Mr. Schofield's letter of Jan. 16. It is only in subacute intestinal obstruction, which may or may not occur postoperatively, that an intestinal hurry has been demonstrated using methylene-blue. Two charcoal biscuits taken orally have also been employed to demonstrate this faster intestinal transit time. The latter material does not diffuse and the same results occur.

London, W.1. J. J. SHIPMAN.

TOLBUTAMIDE IN THE TREATMENT OF ANGINA PECTORIS

SIR,—We were most interested to read the report of Professor Singh and Professor Bardhan (Dec. 19) on progressive improvement in angina pectoris in 9 diabetics and 15 non-diabetics treated with tolbutamide. Of interest to us, also, was their observation that the beneficial effect of the drug was not directly related to its hypoglycæmic effect.

Early in our work with sulphonylureas we noticed that patients given tolbutamide experienced a feeling of general stability and wellbeing which was not related to the hypoglycæmic action of this compound, since it was observed even in those patients whose hyperglycæmia and glycosuria were not improved by such therapy. It was also observed that shortly after institution of tolbutamide therapy some patients suffering from angina pectoris experienced an unanticipated relief from their painful attacks and were able to reduce or to eliminate entirely the use of nitroglycerin. These studies were reported [1] in May, 1958. Subsequently, we noted that patients afflicted with intermittent claudication were also benefited by the use of tolbutamide, as shown by marked increase in claudication time or even complete disappearance of the pain on walking.

In a paper which is now in press (*New York State Journal of Medicine*), we reported on a group of 41 patients with angina and/or claudication treated with tolbutamide for periods of twelve to forty-two months. Among them were 18 suffering from angina pectoris, 20 with intermittent claudication, and 3 with both conditions. 5 patients were given tolbutamide in conjunction with insulin, and the other 36 tolbutamide without insulin. Relief from pain was obtained in 16 patients with angina, in 15 with claudication, and in the 3 patients suffering from both conditions. However, we should like to emphasise that in all our patients who were relieved from pain of angina and/or claudication, the drug had no effect on the associated cardiovascular disorders. Specifically, it did not lower the blood-pressure in 10 patients with hypertension, and failed to prevent myocardial infarction in 2 and diabetic gangrene which necessitated an above-the-knee amputation in 1 patient.

Following the successful use of tolbutamide in diabetics with angina and intermittent claudication, we employed this drug in such conditions in 8 subjects with latent diabetes—that is, subjects with abnormally high glucose-tolerance curves but free from glycosuria and from clinical manifestations of diabetes, and in 10 non-diabetic persons. Beneficial results were noted in both groups, but our series of such patients is

1. Growth at Adolescence. Oxford, 1955.
2. Social Implications of the 1947 Scottish Mental Survey, London, 1953; Berry, W. T. C., Cowin, P. J. *Brit. med. J.* 1954, i, 847; Hammond, W. H. *Brit. J. prev. soc. Med.* 1957, **11**, 131.

1. *Metabolism*, 1958, **7**, 213.

not large enough for a definitive evaluation of the observed benefits.

The mechanism by which the sulphonylureas may produce relief from pain of angina and claudication has not been established yet. Singh and Bardhan state that the benefit in their patients with angina may be accounted for by the reduction of blood-lactic-acid by the drug. One possibility that we have considered in our patients relates to the influence that the drug may have on the metabolism of serotonin and that of adrenaline and noradrenaline. Studies designed to clarify these points are now in progress in patients with angina and/or claudication, and will be reported in a separate communication.

Department of Medicine, New York University Post-Graduate Medical School, New York.

MAXIMILIAN FABRYKANT
BENJAMIN I. ASHE.

CHRISTMAS FACTOR IN THROMBOTEST

SIR,—Dr. Nour-Eldin (Dec. 12) repeats his claim that the thrombotest is not sensitive to Christmas factor. I can only reply by giving the evidence on which I base my contention that it *is* sensitive.

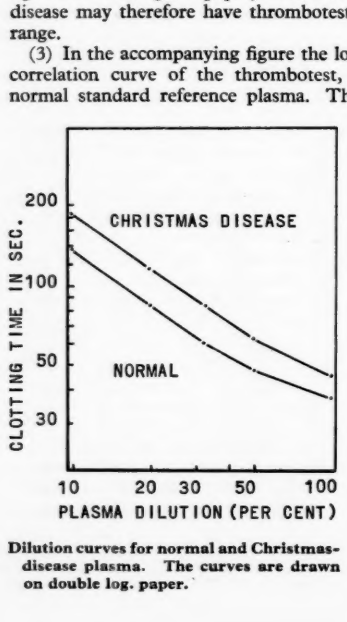
(1) Fig. 4 in my paper (Nov. 7) shows a dilution curve for plasma from a patient with Christmas disease. This experiment was designed to imitate the effect of a disproportionate reduction of the Christmas factor during anticoagulant therapy. The experiment shows that the thrombotest is sensitive to Christmas factor under these conditions.

(2) The following figures give the results of thrombotest estimations in 10 patients with verified Christmas disease, all with characteristic joint bleedings:

Case	*Christmas factor*	*Thrombotest*	*Case*	*Christmas factor*	*Thrombotest*
1	1·5%	63%	6	<1·0%	38%
2	1·0%	72%	7	<1·0%	48%
3	1·0%	44%	8	<1·0%	60%
4	<1·0%	72%	9	<1·0%	48%
5	<1·0%	65%	10	<1·0%	62%

Patients 1–5 were studied at the Institute for Thrombosis Research, the University Hospital of Oslo, and patients 6–10 by Dr. Inga Marie Nilsson, the University Hospital (Almänna Sjukhuset) of Malmö, Sweden. These studies show that the thrombotest gives abnormally low results in these patients. However, I agree that the test is not sensitive to Christmas factor when the concentration of this factor is above 10% (see fig. 4 in the original paper). Patients with mild Christmas disease may therefore have thrombotest values in the normal range.

(3) In the accompanying figure the lower curve is the usual correlation curve of the thrombotest, obtained by diluting normal standard reference plasma. The upper curve shows the result obtained when plasma from a patient with severe Christmas disease (Christmas factor less than 1%) is diluted in the same manner. The difference between the two curves indicates the sensitivity to Christmas factor at different levels of the other clotting factors. The two curves differ by about 50%—in other words, if the Christmas factor is reduced out of proportion to the other factors, the thrombotest value will be as much as 50% lower than it would otherwise be. At a level of 10–20% of the other adsorbable factors, the clotting-times will increase rapidly when the Christmas factor is further reduced.



Dilution curves for normal and Christmas-disease plasma. The curves are drawn on double log. paper.

The thrombotest method is designed for the control of anticoagulant therapy. The main point of interest is therefore the sensitivity to Christmas factor at a low level of the other adsorbable clotting factors. The presented evidence indicates that the test rapidly detects a disproportionate reduction of the Christmas factor during anticoagulant therapy, since the thrombotest times will then increase. For example, if a patient has a reduction of all four factors to 15%, and the Christmas factor then is further reduced, the thrombotest value will drop below the 10% level. This, of course, is exactly the warning the clinician asks for.

Thus, the sensitivity to Christmas factor is definite, but not as high as that of a specific test system. This follows necessarily from the fact that the test is also sensitive to the extrinsic system. Any test which is sensitive to both the extrinsic and intrinsic system must be less sensitive to deficiencies in only one of these systems than specific tests for each system. However, this sensitivity is sufficient for controlling anticoagulant treatment. The thrombotest method has never been recommended as a method for disclosing Christmas disease, nor for the quantitative determination of Christmas factor. For this purpose methods must be used which reflect changes only of the intrinsic clotting system and not a combined test for the intrinsic and extrinsic systems such as the thrombotest.

Rikshospitalet, Oslo.

P. A. OWREN.

HIGH-PROTEIN DIETS

SIR,—In his letter of Dec. 19 Dr. Garrow says that I imply in my paper [1] that a retention of 50 g. of nitrogen does not benefit the cachectic patient. This retention was induced quickly, in 7 days, in surgical cancer patients and did not increase the albumin pool.

As a worker in this field himself this finding should not have prompted such an interpretation from Dr. Garrow. An equilibrium between fixed tissue protein, as judged from body-weight or nitrogen excretion, and plasma-protein has been shown in dogs during both depletion by plasmapheresis [2] and repletion and maintenance by parenteral plasma injection.[3] In each situation, however, a lag period occurred during which "reserve protein" was raided or restored. It is certainly not incorrect to say that "lean muscle mass . . . probably varies with the circulating protein mass," and Dr. Garrow himself has recently shown a concomitant loss of plasma and tissue nitrogen in starved dogs.[4]

The rapidity of turnover and low plasma-albumin observed in two patients with high gastrointestinal malignancy is surely contributed to by gastrointestinal protein leakage, as suggested by Dr. Schwartz and Dr. Jarnum (Dec. 19). I prefer to believe both groups of workers are partially correct: albumin is being "flushed" through the circulation to depleted tissues (Garrow) and being leaked into the gastrointestinal tract from the malignancy (Schwartz and Jarnum). This latter I have referred to as an internal protein shunt. I should still hope to see direct correlative measurements between positive nitrogen balance and net gain in tissue-protein mass to substantiate the former.

Surgery Branch, National Cancer Institute, Bethesda, Maryland.

R. E. MADDEN.

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3. Terry, R., Sandrock, W. E., Nye, R. E., Whipple, G. H. *J. exp. Med.* 1948, **87**, 547.
4. Garrow, J. S. *J. clin. Invest.* 1959, **38**, 1249.

CATHETER DRAINAGE AND INFECTION IN ACUTE RETENTION OF URINE

SIR,—With interest I read the investigations of Mr. Ashton Miller and his colleagues (Feb. 6) in their endeavour to reduce the incidence of infection in patients admitted with acute retention.

The method of sterilising the bottle, which I shall adopt, is excellent and simple, but I feel that the catheter-cum-connector-cum-rubber-tube falls far short of perfection. Although the size of the catheter is not stated, those in common use encourage urethritis and ascending infection by virtue of their size and material. The glass connector is often insecure or dismantled by meddlesome patients, or is pulled on by the heavy and insecurely anchored three feet of rubber tube.

For the past year or more I have been using Gibbon's polyvinyl chloride 'Portex' catheter,[1] which, being five feet long, obviates any glass connections. When passed with the usual aseptic and non-touch technique, urine immediately, by bladder pressure and capillary action, passes down the catheter before there is time to withdraw the obturator. The non-irritating material lying loosely in the urethra minimises urethritis. Air bubbles have little chance of ascending into the bladder, and subsequently the action of the small tube is syphonic.

Although I have not done routine cultures on all patients, it is gratifying to see how many arrive in the theatre with sterile urine, even after ten days.

King's Lynn. J. O. HARRISON.

DANGER OF THE ABBREVIATION P.A.M.

SIR,—In your leading article [2] on organophosphate poisoning, there were a number of references to the use of P.A.M. (pyridine-2-aldoxime methiodide) in the treatment of this condition. I drew attention [3] in 1958 to the danger which might arise in confusing this substance, under this abbreviation, with the much more widely used preparation of procaine penicillin with 2% aluminium monostearate also known as P.A.M., and the type of penicillin used for the treatment of yaws in mass-campaigns. W.H.O. Information Circular No. 2 (January, 1959) on Toxicity of Pesticides to Man (p. 8) also draws attention to the danger of confusing the two preparations, and it has been referred to elsewhere.

South Pacific Commission, Noumea, New Caledonia. THOS. C. LONIE, Acting Executive Officer for Health.

TREATMENT OF TROPICAL EOSINOPHILIA

SIR,—The article by Dr. Baker and his colleagues (Aug. 22) was of particular interest to me, because our own work on similar lines was published in 1958.[4]

151 patients in our series were divided in the following eight groups:

(1) No treatment. Minimum period of observation 1 month, 30 patients.
(2) Diethylcarbamazine 13 mg. per kg. daily for 4 days, 13 patients.
(3) Diethylcarbamazine 13 mg. per kg. daily for 8 days, 6 patients.
(4) Diethylcarbamazine 6 mg. per kg. daily for 4 days, 16 patients.
(5) Diethylcarbamazine 6 mg. per kg. daily for 8 days, 23 patients.
(6) Diethylcarbamazine 3 mg. per kg. daily for 8 days, 17 patients.
(7) Diethylcarbamazine 26 mg. per kg. for 1 day only, 19 patients.
(8) Carbarsone 0·26 g. twice daily for 10 days, 27 patients.

Improvement after treatment was judged on the basis of amelioration of presenting symptoms and the degree of fall in initial total eosinophil-count.

None of the patients in the control group kept without treatment had genuine relief. Diethylcarbamazine was uniformly effective in lowering the total eosinophil-count and in producing symptomatic cure in the majority of patients. Almost all the dosage schedules gave favourable results but minor variations were seen in the degree of effectiveness. We observed that the administration of 6 mg. per kg. of diethylcarbamazine daily for 8 days produced the best results. It is surprising to note how close is this dose to that of 5 mg. per kg. for 7 days recommended by Dr. Baker.

The results in the diethylcarbamazine groups did not differ significantly from those in the carbarsone group. Relief of symptoms, however, was usually felt earlier with the diethylcarbamazine group.

Dr. Baker and his colleagues hint at the possibility of treatment with a single large dose of diethylcarbamazine. We tried a single dose of 26 mg. per kg. and found that this schedule worked equally well.

Medical Division, Atomic Energy Establishment, c/o Indian Cancer Research Centre, Parel, Bombay. R. D. GANATRA.

1. Gibbon, N. *Brit. J. Urol.* 1958, **30**, 1.
2. *Lancet*, 1959, ii, 166.
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4. Ganatra, R. D., Sheth, U.K., Lewis, R. A. *Ind. J. med. Res.* 1958, **46**, 205.

POLIOMYELITIS VACCINATION: DOSAGE AND TECHNIQUE

SIR,—I was interested in a suggestion in your leading article of Jan. 9 that the immunological response to the vaccine in the community may not be so effective as theoretical considerations would indicate. I should like to raise a practical point, small perhaps, though not entirely unimportant, in the carrying out of immunisation programmes.

Personal experience with the difficulties encountered in giving a full dose from a 1 ml. vial in poliovaccination has led me to make inquiries into the literature and to have discussions with colleagues, from which it appears that it is of some importance that the full dose be given. I blamed my ineptitude in getting the full dose out of the 1 ml. vial, but I found that, even with great care, success was sometimes difficult. I was interested to hear from others, who were expert, that they too had had difficulties.

Several authorities (including Salk) are firmly of the opinion that the immunity response is proportional to the mass of antigen injected. It would appear that the important type-1 component of poliovaccine does not always produce a satisfactory immunological response. As with other antigens, individuals vary in the response to a given dose. For these and for other reasons, it is important that the full dose should be given.[1 2]

Independent investigation by the Salford City Analyst has shown that the amount of poliovaccine in the 1 ml. vials was always above 1·1 ml. (The lowest average in the series tested was 1·104 ml.) In other words, there appears to be an "overage" in the vial—as is indeed the stated practice of the manufacturers in conformity with the recommendation of the *British Pharmacopœia*—so the manufacturers have played their part.

Particularly when using the 1 ml. vials, care is needed to see that the subject receives an adequate dose. Losses, some of them almost inevitable under "field" conditions, and in busy surgeries and clinics, may be due to the following causes

The quantity of vaccine left in the nozzle of the syringe after use is surprising in amount, as can be proved by examination of the contents of the barrel after withdrawing the plunger after injection.

There is also a quantity of vaccine left in the needle and holder.

In addition there is loss due to inability to get all the vaccine down from the neck and head of the vial. Perhaps with many volunteers waiting one should not expect that every doctor will spend a long time, which is sometimes necessary, in flicking the whole of the vaccine down.

Some doctors use a special withdrawal needle to draw up the vaccine; here is another possibility of loss.

There is hardly sufficient vaccine in the vial to cover losses when many bubbles have to be expressed.

There may be loss from leakage after inoculation from the puncture in the skin.

1. *Brit. med. J.* 1959, i, 609.
2. *ibid.* 1958, i, 1206.

Experience has shown that under conditions of everyday practice, some volunteers have got less than 1 ml.; occasionally far less than 1 ml.

When it is remembered that different batches of vaccine are known to vary slightly in potency, it is to be hoped that the potency of the vaccine will be increased in future so that even with a smaller dose adequate immunity may still be obtained. Until this is possible, it is wise for special care to be taken in technique in order to reduce avoidable losses in important and costly antigens.

Health Department,
Salford.

J. L. BURN
Medical Officer of Health.

EFFECT OF MODIFIED EGG-YOLK FATS ON BLOOD-CHOLESTEROL LEVELS

SIR,—In a preliminary communication [1] we reported the modification of egg-yolk fats brought about by feeding sunflower-seed oil to hens. A considerable increase (from 5·65% to 30·4%) in the di- and tri-unsaturated fatty acids was noted, and dietary trials of the "unsaturated" eggs in 2 subjects suggested that they might be consumed without raising cholesterol levels above the basal values achieved with a low-fat diet. But Gordon et al.[2] found no difference between the cholesterogenic effects of "normal" and "unsaturated" eggs, when ten yolks per day were fed.

Additional dietary trials have now been carried out using both natural base diets low in fat (4% of calories) and the liquid-formula type of diets. Our subjects were healthy medical students and interns who carried on with their normal activities during the test.

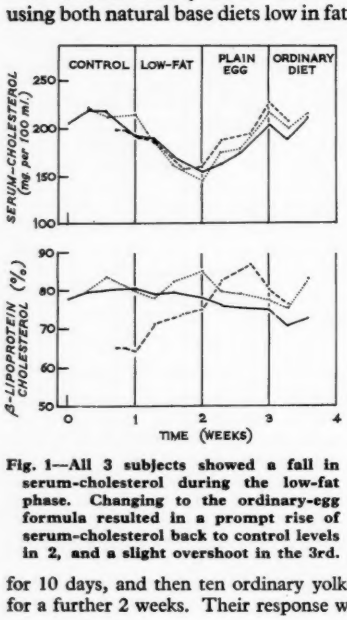

Fig. 1—All 3 subjects showed a fall in serum-cholesterol during the low-fat phase. Changing to the ordinary-egg formula resulted in a prompt rise of serum-cholesterol back to control levels in 2, and a slight overshoot in the 3rd.

Natural food base (low-fat) diet.—Two subjects received the basal low-fat diet for 2 weeks. Ten "unsaturated" yolks were added per day for a further 2 weeks, the diet being held isocaloric by reduction of its carbohydrate content. At the end of this period, the basal low-fat diet alone was continued for 10 days, and then ten ordinary yolks were added per day for a further 2 weeks. Their response was as follows:

Diet	Duration	Serum-cholesterol (mg. per 100 ml.) Subject 1	Subject 2
Control	1 wk.	241	156
Low-fat basal	2 wk.	180	124
Basal plus 10 "unsaturated" yolks per day	2 wk.	244	165
Low-fat basal	10 days	195	128
Basal plus 10 plain yolks per day	2 wk.	250	179

Although no striking differences were seen between the "unsaturated" and ordinary eggs, the rapid rise in cholesterol levels which ensued when subject 1 received ordinary eggs (return to control values in 4 days) and the high final cholesterol levels in subject 2 might be significant. Accordingly, a trial using formula diets was carried out.

Formula diets.—The formula base is that described by Beveridge et al.[3] Egg yolks were added to supply 40% of the calories from fat. This was equivalent to twenty-four yolks per day or approximately 6·6 g. of cholesterol per day. The results of two sets of trials using three different subjects in each group are shown in the accompanying figures.

Despite a sixfold increase in the di- and tri-unsaturated fatty acids of the yolk, there was no significant difference in cholesterogenic effect, compared with ordinary yolks. It should be pointed out that the feeding of sunflower-seed oil to hens does not reduce the cholesterol content of the yolk.[4] Our subjects, therefore, received large amounts of cholesterol (2·75 g. per day with ten yolks or 6·6 g. per day on the formula diet). Egg yolks are known to have a very potent cholesterogenic effect. Equivalent or even much greater amounts of crystalline cholesterol added to the diet have little or no effect on serum-cholesterol levels.[5] The possibility therefore exists that this effect of egg yolks could be due to (1) a fatty-acid factor, (2) a phospholipid, or (3) lipoprotein-cholesterol factor.

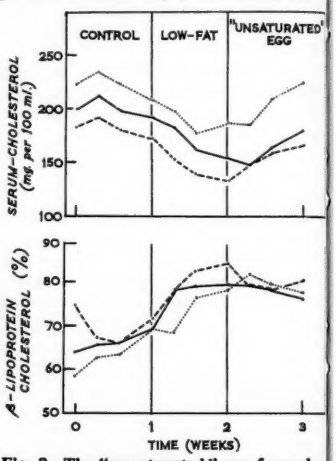

Fig. 2—The "unsaturated"-egg formula resulted in a slower rise in serum-cholesterol which did not quite return to control levels in 2 subjects. β-lipoprotein cholesterol rose during the low-fat phase and again on the egg-yolk diet

Although the unsaturated-fatty-acid content of our experimental eggs did not approach the optimum ratio postulated by Keys,[6] the changes were substantial enough to have shown some effect if this ratio were crucial. It seems far more likely that the hypercholesterolæmia resulting from egg yolk is related to their phospholipid content. Corwin,[7] Steiner and Domanski,[8] and Messinger et al.[5] suggested that the high "lecithin" content of yolk might be responsible. More recently Mustard [9] reported that liver extracts rich in phosphatidyl ethanolamine and containing 0·1% cholesterol produced hypercholesterolæmia and atheroma in rabbits. Beveridge [10] reported that the addition of very small amounts of cholesterol to an "inactive" fraction of butter oils restored its cholesterogenic potency. The possibility that some specific factor such as a phosphatide might act to enhance the effect of egg-yolk cholesterol would explain our results adequately. Eggs are a rich source of phosphatidyl ethanolamine. Reduction of the cholesterogenic effects of eggs might therefore be achieved by alteration of the phosphatide content or by a great reduction in the cholesterol content. Experiments in this direction are now under way.

Departments of Medicine and
Poultry Husbandry,
University of Saskatchewan,
Saskatoon, Canada.

LOUIS HORLICK
J. B. O'NEIL.

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SEVERE HYPERSENSITIVITY TO SULPHAMETHOXYPYRIDAZINE

SIR,—Discussing this condition in their article of Jan. 23, Dr. Maher-Loughnan and Dr. Tullis say that "Side-reactions are slight and uncommon . . . no serious sensitivity reaction had been reported". They make no reference to similar reactions that have already been reported, and readers may have gained the impression that side-reactions to sulphamethoxypyridazine are relatively rare.

This is contrary to accumulating evidence, and I think it may be interesting to recall that in a series [1] of 85 patients taking the drug, reactions occurred in 13. In 1 patient it was a severe generalised bullous and ecchymotic eruption, much like that described by your contributors. These and other cases indicate that sulphamethoxypyridazine causes side-reactions in more than 10% of cases, and severe bullous dermatitis seems to be an occasional feature.

Edinburgh. B. K. HAREENDRAN NAIR.

POLIOMYELITIS: A DANGER FOR VISITORS TO NIGERIA

SIR,—From this hospital there has recently been flown to the United Kingdom a young European with poliomyelitis, on a respirator and attended by a medical and nursing team. Three weeks before, a team of doctors and nurses with a respirator had flown to the north of Nigeria to bring this young man into hospital here. When he arrived he could move only the muscles of the eyes and lids. During the three weeks it has been my privilege to watch the treatment of this young man, which I do not think could have been bettered in any other hospital that I know of. When he left here this patient was able to use his facial muscles, could move fingers and toes, and could be independent of the respirator for about four minutes at a time. This kind of case is met with not infrequently here, always in Europeans; sometimes the outcome has been less encouraging.

Poliomyelitis is virtually unknown in the adult West African, although the late effects of "infantile paralysis" are seen from time to time in children. It seems likely that the indigenous population becomes immunised in early childhood as a by-product of the primitive sanitary and overcrowded living conditions. That such a state of affairs exists in North Africa is suggested by the studies of Paul and Horstmann [2] and in French West Africa by Said et al.[3]

That is one side of the picture. Another is that I have seen in the course of work in the medical outpatient clinic here a number of Europeans recently come to this country who have not been inoculated against poliomyelitis. While travelling here, by sea, I made inquiries of fellow passengers, quite a number of whom were young adults coming to West Africa to teach or to escape the English winter by visiting relatives here. It was a surprise to find that many had not been inoculated. Lagos is only twelve hours by air from London and one reads almost daily in the local newspaper of visits of trade delegations and commercial representatives from Europe. One wonders whether all these persons realise the risks they may be running.

It is possible to get prophylactic inoculation against poliomyelitis in Nigeria but not, of course, as easily as in the United Kingdom. The whole question of the inoculation of visitors and temporary residents is to be taken up here with the Federal Ministry of Health. In the meantime it cannot be too strongly emphasised that prophylactic inoculation against poliomyelitis should be regarded as essential for any European coming to Nigeria even for the briefest of visits.

University College Hospital, Ibadan, Nigeria HAROLD SCARBOROUGH Temporary Honorary Consultant Physician

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THE DIAGNOSIS OF BRUCELLOSIS

SIR,—Your note on my letter last week cannot be allowed to pass without comment for it contains several inaccuracies.

You say that of my 35 proven cases 15 were diagnosed by agglutination tests, 2 by skin tests alone, and 18 by a fourfold rise in titre *after* the skin test (your italics). If you read again the table on pages 88 and 89 of the book *Brucellosis in England* you may see that 14 had an initial agglutination titre of 1 in 80 or higher, 2 of 1 in 40, and 4 more of 1 in 20. (Where you got the figure of 15 from I cannot understand.) Next there were 14 cases where the skin test was positive. 2 of these had already been confirmed by a high agglutination titre; but in 12 (not 2) of them the skin test confirmed the diagnosis. That leaves 9 cases only in which the rising titre after the skin test was the sole laboratory evidence of the disease.

You also say that you have seen no convincing evidence to justify my interpretation of this phenomenon. May I refer you to the paper by Barrett and Rickards [1] which has now become a classic? They say:

"The results of this investigation would seem to indicate that intracutaneous injection of brucellin in non-sensitised persons does not provoke a significant antibody response, and that a rise in titre of brucella antibodies after brucellin indicates previous or current infection."

Then you depart into the upper regions of fantasy by saying that some of my cases may be psychosomatic and some P.U.O.S. Words fail me! It is just because difficult cases have in the past been condemned to such so-called diagnoses that I am fighting this battle. P.U.O. (pyrexia of undetermined origin) is not a diagnosis, though many patients present with it. Granted that some of my patients had obscure pyrexia and also proof that they had at some time been infected with brucella surely it is reasonable to assume that there is some connection between the two. I hold that it is a reasonable assumption and that in such cases the therapeutic test on which you pour such scorn might well be justified. Now for psychosomatic ailments. This diagnosis is popular just now especially in the higher realms of academic medicine, but it is not really a diagnosis, merely a label which explains little. We all know that the psyche may affect the soma and vice versa, and never more so than in brucellosis. Robinson and Evans [2] say:

"A common feature of chronic brucellosis is the lack of abnormalities to be found in physical examination. When the mild symptoms described occur in a patient with no apparent physical abnormality, the picture represents that classified as psychoneurosis."

Harris [3] says:

"The patient with the chronic illness, even though febrile and with demonstrable pathology and positive cultural findings, often presents the picture of radiant health. The expression 'You feel so sick but you look so well' is frequently used by family, friends, and physicians, with the implication that the patient is a psychoneurotic if not a malingerer."

And Harris and Kemple [4] conclude:

"The demonstration of psychoneurosis or psychosis is not a sufficient basis for the dismissal of a diagnosis of brucellosis, nor is the converse true. They are not mutually exclusive; indeed there may be a definite interrelationship."

I do not feel you are justified in saying "Many physicians will be unconvinced by the diagnosis in at least half the

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3. Harris, H. J. Brucellosis (Undulant Fever). New York, 1950.
4. Harris, H. J., Kemple, C. *Psychosomat. Med.* 1954, **16**, 414.

patients". If you had said "Many *pathologists*..." I would not quarrel with you. In common with most students of this disease I have been trying to press the point made so well by Barrett and Rickards:

"We emphasise the fact that the diagnosis of chronic brucellosis is in the hands of the physician, and that until some simple and reliable ancillary investigation is elaborated, the results of the clinical examination of the patient should not be obscured by placing too much faith in bacteriological investigation."

Where this advice is not taken cases will continue to be missed. It is sad that a journal of your standing should contribute to the perpetuation of such mishaps.

Bath. HUGH WALLIS.

*** As we implied last week we were not certain that we had correctly extracted the information we wanted from the 35 detailed case-histories in Dr. Wallis' book, and we are grateful to him for these figures. But they do not dispel our doubts about accepting the skin test alone as the sole confirmatory evidence (in 12 cases); and it is hard to see how the passage from Barrett and Rickards' paper, with its reference to "previous or current" infection, answers the questions we raised about the significance of a fourfold rise in titre after injection of brucellin.

We assure Dr. Wallis that we were not offering "psychosomatic ailments" and P.U.O. as satisfactory diagnoses. No-one would deny that some patients whose illnesses remain unidentified under such labels have in fact got brucellosis, and Dr. Wallis has done an important service in emphasising this possibility. But he will not, we think, on the evidence in his book, persuade his readers—clinicians, pathologists, and others—that he has proved his point in anything like all the cases he records.—ED. L.

FATALITIES AND SPORT

SIR,—*Another rugby football fatality!!!* On Wednesday, Feb. 10, a 22-year-old student playing in an intercollege game was knocked unconscious in a tackle and died on Friday after being operated on for a brain injury. Do all the fanatical anti-boxing enthusiasts not agree and wish to raise their voices in protest to call for the abolition of this very dangerous and occasionally fatal sport? Or do they on the contrary wish to draw a veil over the incident and continue to regard boxing as the only sport which ever produces death?

London, S.W.16. F. H. TAYLOR.

PRIVATE PATIENTS IN THE NATIONAL SCHEME

SIR,—To those who have regarded the denial of free drugs to the private patient as a rank injustice your annotation of Feb. 13 comes as an unpleasant shock: the arguments sustained therein appear to me devious and of doubtful validity, but as one cannot doubt its essential integrity and freedom from political bias, I, like many others, are prepared to be further instructed.

How a private patient not registered on any doctor's list—thereby saving the country a capitation fee—making use of a private doctor's services in any way interferes with the service given by National Health practitioners is difficult to see, and likewise it is difficult to understand how such a doctor is to be regarded as having "entered the Health Scheme" by prescribing to his patient, under proper safeguards, those drugs which are the patient's right, having regard to the latter's contribution, often excessive, to the general body of taxation, out of which the Health Service is maintained.

If he does get better service, and this may not necessarily be the case, then the greater is the spur to see that facilities for patient care in the Health Scheme are improved and this tangible criterion is in my view infinitely worth preserving. If it was a case of too much money chasing too few goods (doctor's services) a case could be made, but as the supply of doctors is likely to exceed the demand, if present student entry is maintained, no strength is added to the argument on this score.

Again reference to the private hospital bed as an "apparent exception" can bring no joy to B.U.P.A. and other allied excellent schemes, as these provide for private nursing-home and private hospital bed facilities and for the private services of surgeons and specialists, and if argument as construed in your annotation is to be consistent then these schemes are against public policy. This I cannot believe, but if persisted in, I can only draw the conclusion that *The Lancet* is out of step with the views of the thousands of provident and thrifty people who support such schemes.

It could, of course, be argued that a doctor having a National Health practice and some private patients not registered with any doctor might be tempted to give a different level of service to the latter, but this surely does him a gross injustice, and in any case the annotation specifically refers to "purely private doctors".

Reference to "buying and selling" medical care merely confuses the issue: the fact is that services and drugs purchased with our money should be available to us as of right, and with it the right to make use of them in part or in whole as specifically promised by Mr. Bevan, when he became the first Health Minister, and this has been denied with a blatant cynicism which seems to afflict all Governments whatever their political colour.

London, S.W.1. ROBERT CUTLER.

SIR,—It is to be hoped that your annotation will produce more thought and discussion than was shown when this subject was last raised in the *British Medical Journal* in November, 1958. The importance of the issues has been more widely realised in the country now, and despite the Royal Commission report the subject will not lose its importance.

Your assessment of the most serious dangers of creating two standards of service in the N.H.S. is much in accord with our own, but since it is a complicated issue and various aspects are stressed we think it right to qualify and question some of your remarks. Firstly, the view, widely held by supporters and even some opponents of the proposal to provide drugs for private patients, that there is some injustice, is in our opinion erroneous. (We have no strong feelings about Private Practice as the Original Sin of Medicine.) It would be an injustice indeed if anyone were refused access to any one part of the National Health Service, but since in fact the Cohen committee—and age-old practice—have held that consultation and prescribing was one item of service, there can be no real grievance. Those who wish to avail themselves of the amenities of the Health Service must do so on the same terms as hold for the rest of the country. (In fact if you pursue the logic of your argument that having paid once people should not have to pay again, you can gather little solace that the hospital pay-beds are justly run. Those paying "full cost of treatment for private beds" are therefore overpaying and are also harshly treated since they have already paid for this part of the service.)

Secondly, the attitude of the British Medical Association membership is taken too readily for granted to be in support of drugs for private patients. The financial and social implications of the proposal are being more widely realised.

The main danger is, as you say, two standards of service. But you fail to bring out that with the inadequate general-practice organisation the N.H.S. would be even further undermanned in actual medical time, and consequently the second standard would necessarily be even lower than already exists. This is adumbrated in your statement that there would be "a

vested interest in preserving the defects of ordinary medical care". Sectional interests would thus not only gain privilege but be actually operative in depressing the standards available for the community. To establish the " rights " of the few, the " rights " of the many would be jeopardised if not actually sacrificed.

A less easily defined but no less real danger would be the psychological effect on the faith of the country in the N.H.S. " Nationalised " medicine would be the poor man's medicine. Already one often hears " But I'm willing to pay for anything else ", in spite of the fact that most general practitioners give their best and there is comparatively little private practice. If this belief spreads it would be as calamitous for the profession as for the patient. We would be divided into the poor doctors, and those who charge. The vast majority of general practitioners have their future bound up with the N.H.S. and any disparagement or deterioration of conditions in the Health Service will adversely affect the doctors no less.

In addition, the desire to stimulate private practice (an avowed aim of the measure) will largely result in stimulating competition. The cooperation and improved relationship which was noted since the inception of the N.H.S. and the marked diminution of financial competition will once again increase. The weary and slow progress to closer integration amongst general practitioners will be halted and group practice and health centres almost wholly obstructed.

Even if the Royal Commission has envisaged possible changes that would be associated with increased private practice, it is doubtful if such a contingency could be fully covered—and would we then have a further inquiry?

The proposal of drugs for private patients is not merely important in itself, but would in fact emphasise and perpetuate some of the worse features that already exist in the N.H.S. In few places in the world is there such a vast expenditure on the training of individual doctors; certainly nowhere do the doctors or the community reap such poor rewards in the exploitation of their skills. The main defect of general practice is that it is in fact " Ancient Medicine in Modern Society "—and the rest of the health service organisation is based on the general practitioner!

In your leader,[1] Charges for Pay-Beds, you rightly observe: " Reform would be a far more popular process if it never removed anything good until it had provided something better." The proposed changes can hardly be said to merit the title of " reform ". There are dangers in venturing into the untried in organisation. " Freedoms " and " rights " must not be cast away lightly, but so far in the profession we seem to have traded in the substance for the slogan. (In what other circumstances would it be necessary or possible for an outside commercial organisation to set up relief working for doctors?)

Society can ill dispense with the traditional general practitioner, who has an important contribution to make, but we must devise ways of enabling him to meet his obligations to the community and encouraging him to make the contribution which his special knowledge and quondam skills qualify him. The overcrowding and overwaiting in doctors' surgeries, and the overburdening of the doctor himself, will not be alleviated one jot by pressing for this measure.

B. BARNETT
M. BARROW.

Birmingham.

SIR,—Your annotation was so appalling, and so obviously inspired by left-wing bias, that I have decided to cease taking *The Lancet*.

For some years now your journal has done its best to produce disunity within the profession. My anger with it has been simmering for some time and I have now decided that the time has come for me to register my complaint by cancelling my banker's order.

I might add that I run a large working-class practice and that I should probably lose slightly by the fact that my patients will still all remain N.H.S. ones and that the central pool may be reduced if this injustice is put right. It does not alter my conviction that it is grossly unjust and illogical to prevent drugs for private patients when these people are allowed their X-rays free, their hospital service free (including drugs!), and their domiciliary visits. Why pick on drugs as an exception?

Space does not allow me to take up your foolish comments on the hospital beds being rented out by the N.H.S.; your facts are not right here either. No doubt in due course I shall read that there has been a take-over bid for your " rag " from the *Daily Mirror*.

Shoreham-by-Sea, Sussex. ANTHONY PARTRIDGE.

SIR,—I am more than surprised at your assumption that the provision of " free " medicine for private patients would result in two standards of general practice. Perhaps I am fortunate in my colleagues in Bristol, but I have not yet met one who gives less attention to his N.H.S. than to his private patients. In my own waiting-room nobody can distinguish the one from the other.

As private practice keeps up one's standard for *all* patients a doctor will therefore automatically benefit his State patients.

Bristol. H. K. V. SOLTAU.

SIR,—All concerned in improving the standard of general practice will welcome your courageous annotation. Like good wine, the National Health Service will grow richer by increasing its own strength rather than by its dilution.

London, N.W.2. D. S. NACHSHEN.

SIR,—I am surprised that *The Lancet* should indulge in such sophistry as the annotation last week on this subject. The so-called apparent exception is an exception indeed. The private bed in the public hospital rented at an empirical price enables the patient not only to buy the " personal care " of his consulting attendant but also to enjoy the full benefit of free drugs, dressings, and ancillary care which his attendant can prescribe. The statement that payment for personal care within the National Scheme does not exist is only true so far as the general-practitioner service is concerned. In practice it is available to any patient who elects to go under the care of a consultant fortunate enough to control private beds.

London, W.1. JEROME STURRIDGE.

*** To those who believe that medical privileges should not be purchasable within the National Health Service, the defence of private pay-beds in public hospitals can certainly sound a little sophistical. We ourselves have continued to defend them on the ground that, so long as they cost the service nothing, they can be said to be outside it. The wish to avoid having different standards of care within the service is not, of course, confined to people of particular political convictions.

If the proposal were simply that " purely private doctors " should prescribe N.H.S. drugs, we should be less troubled: our objections, though we think them valid, might not be of much practical importance. But an N.H.S. doctor prescribing N.H.S. drugs to someone registered with him as a private patient is unquestionably within the Health Scheme, and grave harm would be done if his patients began to transfer from his ordinary list to his private list in the hope of getting something better for a fee. It is the amenities of the ordinary list, rather than those for the fee-paying patient, that the N.H.S. has a duty to improve.—ED. L.

1. *Lancet*, 1952, ii, 229.

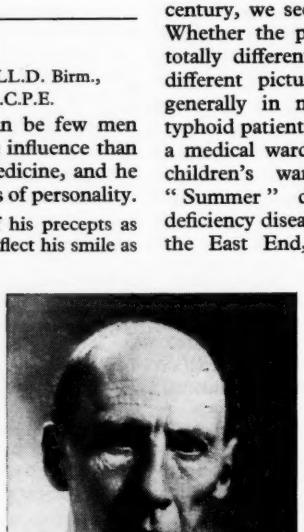
Obituary

ROBERT HUTCHISON

Bt., M.D., LL.D. Edin., Hon. D.Sc. Oxon., LL.D. Birm., Hon. M.D. Melb., F.R.C.P., Hon. F.R.C.P.E.

BEFORE the war we wrote: "There can be few men alive today who have had a more intimate influence than Hutchison on the everyday practice of medicine, and he has achieved it largely by the direct impress of personality.

"All over the world practitioners think of his precepts as they work at the bedside; their faces faintly reflect his smile as they remember his salted sayings, and they are daily saved from imprudence and humbug because they were taught by a man with a sublime gift for common sense."



Press Portrait Bureau

Twenty-one years later, his influence may have been attenuated by passage; but by those who knew him he will always be remembered not only as one of the great clinicians and teachers of our time, but as a man of individual character. Having chosen his role, he played it with the touch of exaggeration needed to make his teaching memorable; and he enjoyed his prejudices. But the ability, the wisdom, the clinical genius, were very real. Moreover, the grave and the gay, severity and kindness, were so joined in him that he could raise standards yet be held in general affection.

He was born at Kirkliston, Midlothian; and one account of him describes a boyhood classically austere, with excess of oatmeal and a four-mile walk to school. Having the kind of early promise that is later fulfilled, he was Ettles scholar at Edinburgh University and senior president of the Royal Medical Society, graduating with first-class honours in 1893. In surgery those were still the days of the carbolic spray; and he afterwards recalled that almost his first duty as a dresser was to give an anæsthetic (chloroform) for a long abdominal operation—having never seen one given before.

After house-appointments in Edinburgh, he worked in Paris and Strasbourg before becoming demonstrator of chemical physiology in the university. In that post, and in 1896 when he took a house-appointment at The Hospital for Sick Children, Great Ormond Street, he produced the earliest of his many papers (a handlist of 276 was compiled by Dr. White Franklin in 1951), his first subjects being the movements of the fontanelle, the state of maternal and fœtal blood at birth, estimation of the alkalinity of the blood, degeneration of brain cells, and, particularly, the chemistry and pharmacology of thyroid secretion. He had a considerable record of research when in 1897 Leonard Hill invited him to The London Hospital as assistant in the physiology department. In the residents' quarters at Great Ormond Street he had already planned and executed with Harry Rainy the first edition of their *Clinical Methods* which remains the guide of so many students, though its editors have changed. With so many outstanding qualifications he was elected in 1900 to the staff of The London and also of The Hospital for Sick Children.

Describing those far-off times, he has remarked characteristically that "looking back through the mist of half a century, we seemed to get on very comfortably indeed. Whether the patients got on as well was, of course, a totally different matter." The wards presented a very different picture from those of today, with diseases generally in more advanced form, and four or five typhoid patients in each ward. In the 1900s, he admitted, a medical ward was a rather depressing place, and the children's wards must likewise have been grim. "Summer" diarrhœas, acute marasmus, and such deficiency diseases as rickets were appallingly prevalent in the East End, with its poverty and ignorance, and Hutchison could have found no more useful interest than nutrition and diet, to which he gave much thought. At a time when authorities elsewhere were complicating the feeding of infants, he preached simplicity, saying that the infant's response is the only valid test of a feeding plan. ("My dear boy, all that you need to know about infant feeding can be written on the back of a postage stamp.") By one of his "premonitions", as Dr. Langley Porter has called them, he made The London Hospital supply mothers with free cod-liver oil to add to the diluted sweetened evaporated milk which was all that many of them could afford for feeding their babies.

In the early years of the century, Hutchison was one of a group of able men at The London who were rejecting the concept of the clinical entity, and, deeply influenced by the biological approach of the German school, were coming to think in terms of maladaptation to environment. Arthur Keith and William Bulloch were his intimates; and there were many other stimulating people in the hospital—Leonard Hill, and Henry Head, and H. M. Turnbull among them. (Turnbull used to relate that on their annual departure to the North for Christmas—in separate carriages—Robert attracted much attention as he paced the King's Cross platform in deerstalker cap, a long caped overcoat, and Mother Hubbard boots—the living image of Sherlock Holmes!)

Born to be a teacher, he reacted to his environment by writing further books, some of them in lecture form and several of them astonishingly successful. *Hutchison's Food and the Principles of Dietetics*, still a standard work, started life in 1900, and *Lectures on Diseases of Children* in 1904. With Stansfield Collier (and later Reginald Hilton) he edited *An Index of Treatment* from 1907. This was the year in which, as an original member of the editorial board of the *Quarterly Journal of Medicine*, he contributed to its first number his famous paper On Suprarenal Sarcoma in Children with Metastases in the Skull. Since 1910, when Homer Wright showed that the cells of these tumours arise from embryonic sympathetic nerve-cells in the medulla, the disease has been called neuroblastoma of the suprarenal medulla (Hutchison's type). In 1908 a handbook on *Applied Physiology* appeared, and in the later '20s it was followed by *Lectures on Dyspepsia*, his London Hospital lectures called *The Elements of Medical Treatment*, and *Some Principles of Diagnosis, Prognosis, and Treatment.*

His ward rounds, with Hutchison a formal and often formidable figure in grey frock-coat, have often been described. What was most important about them, for student and houseman, was the sensitive way in which he dealt with patients, old and young, and the delicacy, the economy, and yet the completeness of his examination.

"To watch him examine an infant, especially one with pyloric obstruction, was an unforgettable lesson in clinical procedure. The gentleness, not only of his manipulations, but also in the spirit of his approach, made one feel that, without sentimentality, the man was alive with sympathy for the suffering child . . . He made his own demonstrations brilliant examples of what to do, and what not to do, in clinical examinations of the patient."

Again there was the frequent evidence of wide and up-to-date reading, so that new knowledge supplemented experience. Diagnosis and prognosis were brought to a fine art. In his earlier days at The London there were, of course, no reports from X-ray department or biochemical laboratory.

"You may say: 'Well, in that case the diagnosis must have been very often wrong.' There, however, you would be in error. It was not, as a matter of fact, often far wrong. The object of diagnosis fifty years ago was chiefly to tell what would be found post mortem, and in that art the physician with his highly developed clinical instinct was extraordinarily skilful."

Dr. Donald Hunter said that of all Hutchison's messages to his pupils this was the greatest—that as Medicine becomes more complicated good clinical method grows rather than lessens in importance.

It would be idle to pretend, however, that only his skill and shrewdness made these occasions memorable: there was also the fascination of watching someone different from anybody else, and listening to his fastidious utterance—fastidious and courteous even in his occasional invective. (Who, as a student, would not enjoy Hutchison's description of his Great Ormond Street clerks as "a curious collection of crapulous cretins creeping from crib to crib", or the comparison of his London Hospital ones to tabetic snails?) Like all good teachers, he took trouble to make his point memorably: when a certain type of squealing, kicking baby came into the outpatient department he would ask, "What is the treatment here?" and getting no answer would say, "Gentlemen, it is a clear-cut case of bromide for the mother." His lectures are full of pearls (as he would not scruple to call them):

"It is quite impossible that you should always be right in your diagnosis, if only for the reason that disease does not always play the game. It is better, however, to be wrong on sound principles than right by chance. Guessing is to be avoided at all costs; for if once you get into the habit of guessing you are diagnostically dammed."

He believed in what some character in *The Wrong Box* calls "judicious levity"—a phrase that came beautifully off his tongue. Urging that nobody should ever start a lecture in his memory, he remarked: "There are better ways of commemorating the dead than by boring the living."

Naturally he himself was asked to give many lectures, including, at the Royal College of Physicians of London, the Goulstonians of 1904 and the Harveian oration of 1931. He was elected president of the college, in succession to Lord Dawson, in 1938, having previously been president of the Association of Physicians and of the Royal Society of Medicine. His scholarship and distinction of mind earned him the highest honours that Medicine can bestow; but in spirit he was neither an administrator nor a man of action and his main achievement was not in such offices. He was created a baronet in 1939 and spent the last part of his life at his home at Streatley-on-Thames. Even during his active years he had been a good deal disabled by a longstanding disorder. "Still," he wrote, "as a disease it has two great merits: (1) it is entirely painless; (2) there is no known treatment. I am therefore spared all modern therapy."

We conclude with a note from W. R. B.:

"Robert Hutchison's character was so complex that almost anything which it seems obvious to say about him needs qualification. He became a doctor before X rays were discovered, and retired from his hospitals at the beginning of the 1930s, before the major therapeutic discoveries of that decade had been made. An exponent of medicine as an art rather than a science, and a brilliant intuitive diagnostician, he had more in common with the 18th century than with the middle of the 20th. He was almost the last of a kind of physician now nearly extinct. Yet his early contribution to dietetics was scientific, and at heart he was far more of a scientist than he allowed his students to know.

"I am not sure whether he invented the classification of doctors into 'winduppers' and 'pooh-poohers', but I have heard him use it. He himself was a 'pooh-pooher' on the largest scale; but this, one felt, was a public persona which he had constructed by elaborating some of his native characteristics. Fortified by his gaunt and lanky appearance, his slow and dignified gait, a grey frock-coat, his Edinburgh accent, and his wit, it was a formidable facade, which might have made him admired and even a little feared. Yet he inspired, particularly in his colleagues and pupils, an affection which earned him the improbable diminutive, Bobbie. Relaxing in the staff-room after a ward round, he would put off the persona as far as he could, address one as 'My dear boy', and chuckle over some anecdote which was 'really very amusing'. Behind the mask there was, I think, a rather shy and lonely man, who, like an ancient Stoic, found life on the whole a bad thing one had to make the best of."

Another of his friends once put forward the opposite conclusion, saying that the pessimism was the mask, and behind it was a mind intellectually gay, with a cordial distaste for the dull. Both views could be sometimes right, for it was his complexity that made him so interesting a person.

Sir Robert Hutchison died at his Berkshire home on Feb. 12, aged 88. He married, in 1905, Lætitia Norah Moore-Ede, M.B. Lond., daughter of the Very Rev. Dr. Moore-Ede. Lady Hutchison survives him with two sons and a daughter: Mr. Peter Hutchison succeeds to the baronetcy. Sir Robert's brother, the late Sir Thomas Hutchison, was Lord Provost of Edinburgh in 1921-23.

In preparing this memoir we have drawn gratefully, though usually without acknowledgment, from tributes which appeared in the *Archives of Disease in Childhood* in October, 1951, and in the *London Hospital Gazette* at various times.

WALTER PATON MacCALLUM

C.B.E., D.S.O., M.C., E.D., M.B. Sydney, F.R.A.C.P.

Dr. MacCallum, consulting physician to the Prince Henry Hospital, Sydney, died on Nov. 22. He had held office in the Royal Australasian College of Physicians as honorary secretary from 1948 to 1950 and as honorary treasurer from 1950 to 1958.

During the 1914–18 war he served in the infantry and staff of the Australian Imperial Force in Gallipoli, Egypt, France, and Belgium and was awarded the M.C. and D.S.O. He was demobilised in 1919 with the rank of major, and returned to Australia

to study medicine at the University of Sydney; and the rest of his medical life, apart from further war service, was spent in that city. After qualifying in 1924 he held house-appointments, and in 1926 he joined the staff of the Royal Alexandra Hospital for Children. In 1934 he was also appointed to the staff of the Royal Prince Alfred Hospital. During the late war he served with the A.A.M.C. from 1940 to 1947 in Palestine, the Western Desert, Greece, Crete, Netherlands, East Indies, and the South-West Pacific. In the later years of the war he acted as deputy director-general of medical services with the rank of brigadier, and for this work he was appointed C.B.E.

He was elected F.R.A.C.P. in 1946, and his published work included papers on rheumatic fever and meningitis in childhood.'

A colleague writes:

" MacCallum belonged to one of the outstanding families in New South Wales, and had, himself, a first-class mind and an attractive manner. He was one of the group of senior physicians who guided the Australasian College along sound lines in its early critical years."

JAMES IGNATIUS ENRIGHT

B.A., M.D. R.U.I.

Dr. J. I. Enright died on Jan. 13 in Dublin. In the 1914–18 war he took part in investigations on pellagra among prisoners-of-war in Egypt.

He was educated at a Jesuit College and the Royal University of Ireland. He graduated M.B. with honours in 1914. After holding resident appointments at the Eastern Fever Hospital, Homerton, and the Royal Sussex Hospital, Brighton, he became medical officer in charge of a prisoner-of-war hospital in Cairo. On his return to Ireland he settled in practice at Dalkey, where he was born.

P. H. M-B., who worked with him in Cairo, writes:

" Enright was then a young, impulsive, loquacious, and witty Irishman with an inquiring mind. Among the wretched, emaciated, and half-starved Arabs and Turkish prisoners he found much to interest him. Pellagra had just made its appearance in many strange and unforeseen guises, and he became familiar with pellagra typhus, and many peculiar actinogenic eruptions on the face, hands, and legs, as well as œdematous swellings. Later he reported these observations and also an equally instructive outbreak of pellagra in the seemingly well-fed and nourished Austrian and German prisoners during 1917 and 1918. (The paintings which were made for him by an Austrian sergeant, who was by trade a sign-painter, are now in my possession.) He also described an unrecorded fatal urinary infection with *Bacterium coli* which was traced to miliary cortical abscesses in the kidneys.

" Ignatius was a fluent and entertaining speaker, with a delightful brogue, and he could quote at length from Latin and English literature. Warm-hearted and generous he was a staunch and loyal friend, and his sudden, unexpected eruptions into the metropolis were always welcome."

DR. WU LIEN-TEH

W. C. W. N. writes:

" Wu Lien-Teh was a remarkable man for he was able to enjoy the best of both worlds—the East with its wisdom and the West with its scientific practice. He held fast to the traditions and philosophy of his forebears despite the many years he spent in Europe and the United States.

" I have reason to be grateful to him for his advice and kindness when I found myself, an occidental, in the orient. We had a common interest in that we graduated from St. Mary's Hospital, and when he visited Hong Kong he would reminisce on his happy student days at Cambridge and in London. He was ever grateful for the friendship of Sir Zachary Cope and Prof. T. R. Elliott.

" Most of us start contemplating retirement after the age of 60, but not Wu Lien-Teh. I travelled with him and his family in 1937 from Hong Kong to Singapore after the Japanese had overrun Shanghai. His beautiful home and valuable collection of ancient Chinese medical books had been burnt. I recall his fervour when he said: 'I am 60 and have lost everything but I shall not give up medicine. I shall open a dispensary in Malaya.' Ironically he was to suffer from the Japanese again a few years later when they occupied Malaya. Undaunted he started to practise again after their defeat.

" He more than any other Chinese, laid the foundations of a modern medical service for his country. It is fortunate that posterity will have in his autobiography—*Plague Fighter*—a record of the achievements of this great doctor."

DR. EILEEN HICKEY

P. F. writes:

" Several generations of students of the Belfast School of Medicine were well acquainted with Dr. Hickey's tireless energy in social, religious, and political fields, but it is as a clinical practitioner, teacher, and adviser that she will perhaps longest be remembered.

" As a clinician she was infinitely patient and painstaking, shrewd and wise. Her experience extended over four decades of change, and she could accept with equanimity the encroaching tide of medical advance, with its bright if rather brittle purveyors of the ' scientific approach ', absorbing the principles as a good doctor should, but never losing her sense of perspective. The student body were ever her particular concern: their deportment, manners, dress—little escaped her vigilance, and on their application and training she often expressed herself strongly. Her clinical clerks usually found that she did not suffer fools gladly, but they left her firm richer and wiser for the experience.

" For some time she had been troubled by a partial deafness; but this affliction only sharpened her clinical acumen. ' Had I my way,' she snorted to a student, advancing on a patient whilst producing the inevitable stethoscope, ' that instrument would be banned during your first clinical year: then perhaps you would use your eyes! ' Or again ' We make mistakes, not because we don't know, but because we don't look.' She looked: and saw her patients, as well as their illnesses; she saw her students as beginning an odyssey; she saw her profession in its nobility, and her life as an opportunity to serve."

Public Health

Infectious Diseases in England and Wales

Disease	Week ended January				
	2	9	16	23	30*
Diphtheria	6	5	3	6	8
Dysentery	728	840	781	864	1092
Encephalitis:					
Infective	4	3	1	3	2
Postinfectious	..	1	..	2	2
Food-poisoning	182	134	139	192	183
Measles, excluding rubella	1504	1407	1049	1069	1200
Meningococcal infection	23	19	20	18	27
Ophthalmia neonatorum	21	16	16	32	19
Paratyphoid fever	9	7	2	3	4
Pneumonia, primary or influenzal	373	420	337	341	430
Poliomyelitis:					
Paralytic	7	2	10	4	5
Non-paralytic	3	2	2	1	1
Puerperal pyrexia	156	189	179	196	234
Scarlet fever	1182	802	933	1189	1265
Smallpox	..	..	..	..	..
Tuberculosis:					
Respiratory	396	399	446	449	393
Meninges and C.N.S.	4	3	3	6	4
Other	37	51	48	48	56
Typhoid fever	1	2	..	..	1
Whooping-cough	521	675	740	884	967

* Not including late returns.

Parliament

Scottish Mental Health Bill

ON Feb. 9, in introducing this Bill, which has already been briefly described in our columns,[1] Mr. JOHN MACLAY, Secretary of State for Scotland, said that it had three main threads; to retain the best features of the existing law, to weigh the balance wherever there was doubt in favour of the liberty of the subject, and to devise a code which was in harmony with authoritative medical opinion.

Miss MARGARET HERBISON welcomed the Bill on behalf of the Opposition with two reservations. She regretted that responsibility for the training and occupation of the so-called "ineducable" children should be transferred from the education to the health authorities, and she was uneasy that the local authorities' powers to provide community mental-health services were only permissive and not mandatory. These new services would place a heavy burden on the authorities and she asked what financial help would be given to them.

Uncertainty about the local-authority services was a recurrent theme in the debate (which was interruped for three hours for a discussion on the breakdown of the Cyprus talks). Mrs. JUDITH HART pointed out that the authorities already had most of the powers necessary to give community care to the mentally ill and the mentally defective, but made disappointingly little use of them. For instance, out of 49 Scottish county councils and large boroughs only 1 had appointed a special committee to deal with mental health. Too few child-guidance clinics had been provided, and those that existed often had no consultant psychiatrist or psychiatric social worker on the staff. There were only 2 senior medical officers in Scotland engaged wholly in mental-health work. Of the 118 welfare and mental-welfare workers in the Scottish counties 70 were also district clerks, and probably only half their time could be given to their mental-welfare duties. 5 psychiatric social workers were employed in the whole of Scotland, but not all 5 were fully qualified. Mental-health work would not progress until the authorities' powers were translated into duties.

Dr. J. DICKSON MABON suggested that if the Government persisted in their present attitude towards finance we should be no better off with the passage of the Bill. For twelve years the local authorities had had permissive powers, and the Secretary of State had been able at any time to direct that they should become duties. Yet the Fyfe Committee had severely criticised the administration of the mental-defective service in 1957 and precious little had been done since.

Mr. T. G. D. GALBRAITH, joint under-secretary of State for Scotland, said that the Bill set the legal foundation for the things to be done in terms of care, treatment, and aftercare. It did not itself provide the accommodation or recruit the workers. These services were all the responsibility of various agencies, and the Bill laid down only the law under which they would work. Therefore, it did not require substantial new charges. They looked to the local authorities to play a large part in the expansion of the mental services outside the hospitals and within the community. The expansion would certainly involve considerable expenditure, and he assured the House that it would be taken into account in the discussions on the general grant for local authorities which would be held later this year. He recognised that this arrangement did not altogether satisfy all hon. Members and that there might be differences of opinion as to the best way of financing local-authority services.

There were several reasons, he continued, against making the local authorities' powers permissive rather than mandatory. Not all authorities had the same potential for expansion, and any statutory duty would therefore have to be limited to what the smallest authority could manage. If local democracy was to mean anything authorities must at least be given the chance to exercise initiative. Again, for the rest of the health service the authorities' powers were permissive, and the Government was anxious that the mental and physical health services should be treated in the same way. Dr. MABON pointed out that the mental-health services were not at the same stage of development as these for physical health. But Mr. GALBRAITH maintained that we must have permissive powers for both at a time when we were trying to make the two types of medicine comparable.

1. See *Lancet*, Jan. 30, 1960, p. 290.

QUESTION TIME

A Seat in the Cabinet?

Mr. L. A. PAVITT asked the Prime Minister if, in view of the negotiations with the medical profession following the publication of the report of the Royal Commission on Dentists' and Doctors' Remuneration and the importance of the Government's decisions arising therefrom, he will enlarge the Cabinet by the inclusion of the Minister of Health. Mr. R. A. BUTLER replied: The hon. Member would be wrong if he thought that, because the Minister of Health is not a member of the Cabinet, the Government will give less than due attention to the questions raised by this report. Mr. PAVITT: Will the Leader of the House urge the Prime Minister to take into consideration, not only the Government's position *vis-à-vis* the Minister, but, in view of these negotiations with the medical profession, the need for confidence on the other side in the negotiations if the outcome is to be satisfactory? The report may well set the pattern of the family doctor service for the next twenty years. The way in which previous negotiations were carried on destroyed the confidence of the medical profession. This single act perhaps would be sufficient to restore confidence in the Government. Mr. BUTLER: The hon. Member's question will have done a service if it draws attention to the fact that the Government attach the greatest possible importance to this Commission and to the findings. I can assure the hon. Member and the House that this matter will be treated by the Government as one of the first importance.

New Drugs

Mrs. HARRIET SLATER asked the Minister of Health what proposals he had for controlled research and testing of new drugs before they were sold without a doctor's prescription.—Mr. DEREK WALKER-SMITH replied: While there are powers which enable supply to be permitted only on medical advice and prescription there is no authority under existing legislation for this requirement. The Committee on the Cost of Prescribing has, however, made a recommendation that all new drugs should be subjected to clinical trial, and I hope soon to be able to reach a decision on it.

Drugs for Private Patients

Dr. DONALD JOHNSON asked the Minister what undertaking was given by the British Medical Association, in making its representations to him last year about the desirability of supplying drugs under the National Health Service to private patients, to cooperate in the administration of safeguards against over-prescribing on the part of private doctors.—Mr. WALKER-SMITH replied: In discussions with officers of my department on the possibility of making the kind of financial and administrative arrangements which would be required if it should be decided as a matter of policy to introduce legislation, the Association agreed to safeguards on similar lines to those applying under the National Health Service.

Sabin Oral Vaccine

Mr. W. G. CLARK asked the Minister whether it was intended that there should be trials of Sabin oral poliomyelitis vaccine in this country.—Mr. WALKER-SMITH replied: The Medical Research Council will shortly be carrying out small-scale trials of this vaccine in selected areas and I am asking the local health authorities concerned to give their full cooperation.

Employment of Disabled

Of the 695,000 registered disabled just under 60,000 were registered as unemployed in January.

Control of Drugs

The Poisons Board have recommended that the following substances, as well as 'Preludin', should be made available only on medical prescription:

Acetylcarbromal
*Androgenic and œstrogenic substances, the following:
Benzœstrol
Steroid compounds with androgenic or œstrogenic activity; their esters
Derivatives of stilbene, dibenzyl or naphthalene with œstrogenic activity; their esters
Azacyclonol; its salts
Benactyzine; its salts
3-Benzylhydrazinocarbonyl-5-methyl*iso*oxazole; its salts
Bromvaletone
Captodiame; its salts
Carbromal
2-*p*-Chlorophenyl-3-methylbutane-2 : 3-diol.
Guaiphenesin.
4-Hydroxymethyl-2 : 2-di*iso*propyl-1 : 3-dioxolan.
Hydroxyzine; its salts.
Imipramine; its salts.
Mephenesin; its esters.
Meprobamate.
Metformin; its salts.
Methocarbamol.
α-Methyl-phenethylhydrazine; its salts.
Methyl phenidate; its salts.
Nialamide; its salts.
Phenelzine; its salts.
Phenformin; its salts.
Pipradol; its salts.
Rauwolfia, alkaloids of; their salts.
Thalidomide; its salts.
Zoxazolamine; its salts.

* Except preparations intended for use in external applications and animal feeding stuffs.

Medicine and the Law

Probation for Schizophrenic

AN 18-year-old youth, who pleaded guilty to stealing over £15,000 from the city treasurer's department at Norwich whilst employed as a clerk there, has been put on probation for three years.[1]

Dr. William Abel, of Hellesdon Hospital, said in evidence that the youth was a typical schizophrenic. The prison medical officer, Dr. B. M. Tracey, agreed with most of Dr. Abel's findings.

In putting this offender on probation, Mr. Justice Byrne said: "You have pleaded guilty to an extremely serious offence which would merit many years of imprisonment in normal circumstances. But two doctors agree that you are mentally ill. . . . If I sent you to prison, you would probably become a criminal."

It is a condition of the probation that he goes to a mental hospital for twelve months.

No Home for an Epileptic

The policy of the courts in dealing with first offenders is to avoid giving a prison sentence unless this is clearly indicated by the seriousness of the offence or for some other reason. It is strange, therefore, that the Nottingham magistrates should have found that they had no option but to remand a pregnant woman suffering from epilepsy to prison for three weeks for what may be described as welfare reasons.

The woman, aged 27, had pleaded guilty to stealing £12 10*s.* from a wallet in a shop.[2] She took the money, handed the empty wallet back to the owner, and later took most of the money back and said she had spent £1.

On her third appearance in court, it was reported that four epileptic colonies had refused to have her because of her pregnancy, and a mother-and-child home had refused to have her because she was considered unstable in view of the epilepsy. Her husband had been sentenced to two years' imprisonment three days after they married.

Ordering that the case should be sent to the Home Secretary, the chairman of the bench said that there had been "a grave lack of responsibility on the part of certain branches of the medical services". Remanding the woman to prison was the only way of ensuring that she received proper medical attention.

1. *Guardian*, Feb. 11, 1960.
2. *Guardian*, Feb. 13, 1960.

Diary of the Week

FEB. 21 TO 27

Monday, 22nd

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Attempted Suicide.
GUY'S HOSPITAL, S.E.1
5.30 P.M. Prof. W. J. H. Butterfield: Diabetes Mellitus.
HUNTERIAN SOCIETY
8.30 P.M. (Mansion House, E.C.4.) Mr. C. R. Rudolf: New Light on William Clift and His Contemporaries. (Hunterian oration.)
MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice.* Dr. M. C. G. Israëls: Pitfalls in the Diagnosis and Management of Blood Diseases.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Queen's College, Dundee.) Dr. H. B. Goodall, Dr. William Walker: Megaloblastic Anæmias.

Tuesday, 23rd

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Prof. D. E. Denny-Brown: Diseases of the Basal Ganglia and Their Relation to Movement. (First of two Croonian lectures.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine.* Dr. Graham Hayward, Dr. Mary Barber, Dr. John Goodwin: Bacterial Endocarditis.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. W. R. S. Doll: Epidemiological Methods in Leukæmia Research.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. S. L. Szur: Radiotherapy in Dermatology.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Mr. Kenneth McLay: Tests of Acoustic Function (I).
MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) Dr. J. N. Mills: J. S. Haldane. (University lecture.)
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. J. A. Sharp: The Rhinencephalon.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Prof. R. E. Coupland: Basic Methods in Histochemistry.

Wednesday, 24th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. A. E. Mourant: Significance of Human Blood-group Distribution.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Laboratory Diagnosis of Mycotic Lesions.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. Paul Wood: Chronic Constrictive Pericarditis.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
5.30 P.M. Mr. McLay: Tests of Acoustic Function (II).
MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) *Medicine.* Dr. R. W. Luxton: The Common Health. (Presidential address.)
UNIVERSITY OF ST. ANDREWS
4 P.M. (Queen's College, Dundee.) Dr. H. B. Goodall: Hæmolytic Anæmia in Pregnancy.

Thursday, 25th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Professor Denny-Brown: Diseases of the Basal Ganglia and Their Relation to Disorders of Movement. (Second of two Croonian lectures.)
UNIVERSITY OF LONDON
5.30 P.M. (Royal Free Hospital School of Medicine, 8, Hunter Street, W.C.1.) Dr. Sybil Cooper: Relations Between the Histology and the Physiology of Muscle Stretch Receptors.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. Sheila Sherlock: Liver Failure.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. F. Ray Bettley: Lupus Erythematous.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
5.30 P.M. Mr. McLay: Tests of Vestibular Function (I).
MANCHESTER MEDICAL SOCIETY
8 P.M. (Staff House, University of Manchester.) *Anæsthetics.* Dr. Tom Dinsdale, Mr. G. V. Ashcroft, Dr. W. Ken Jones: Dental Anæsthesia.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Prof. A. C. Frazer: Diagnosis, Pathogenesis, and Treatment of Defective Intestinal Absorption.

Friday, 26th

ROYAL SOCIETY OF MEDICINE
5 P.M. *Pædiatrics:* Dr. Mary Sheridan, Mr. Gavin Livingstone, Mr. Michael Reed, Miss W. Galbraith: Hearing and Speech Disorders in Childhood.
8.15 P.M. *Obstetrics and Gynæcology.* Mr. V. B. Green-Armytage, Mr. M. D. Arwyn Evans, Mr. D. S. Perchard: Hypnosis in Obstetrics and Gynæcology.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Professor Sherlock: Diagnosis and Treatment of Portal Hypertension.
4 P.M. Dr. Fraser Roberts: Medical Genetics.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
5.30 P.M. Mr. McLay: Tests of Vestibular Function (II).
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
4.30 P.M. Dr. John Foley: Hypertonus and Hyperreflexia.
MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, W.1
7.30 P.M. Dr. G. L. McElligott: Venereal Disease and the Public Health.

Notes and News

EFFECT OF RADIATION ON HUMAN HEREDITY

IN some widely scattered areas of the world the level of natural background radiation is well above that in other parts of the world, and properly planned studies of the populations in such areas could make significant contributions to knowledge of the genetic and somatic effects of prolonged exposure to low levels of radiation. The recent report [1] of the W.H.O. expert committee on radiation surveys the known areas of high background radiation and sets out the principles of planning investigations of such areas. The Kerala area, at the southernmost extremity of the west coast of India, is probably the only area now known which might be profitably investigated, and the last part of the report is devoted to the application of the general principles to the planning of what is called "the Kerala project".

Comparison of specific mutant phenotypes in the irradiated and control populations will rarely be feasible, and reliance will usually have to be placed on a comparison of populations with respect to those characteristics that are assumed to reflect the cumulative effect of mutation at many loci. The committee make a number of suggestions concerning information to be collected in the Kerala project, with particular reference to the ad-hoc census that would have to be the first step; and a brief section of the report is devoted to the estimated requirements in men and material.

HOSPITAL PLANNING AT WOLVERHAMPTON

THE Birmingham Regional Hospital Board and the Wolverhampton Hospital Management Committee have been considering plans for the expansion of hospital services in the Wolverhampton group. A scheme has been proposed by which the number of beds at the Royal Hospital will be reduced to about 250 and the hospital will become a centre for casualties and outpatients on the lines of a policlinic with some inpatient beds. The orthopædic department and some orthopædic beds will remain and other services will include radiology, physiotherapy, and pathology. A new radiotherapy department will be added, with a cobalt unit and isotope and physics department. There will also be some radiotherapy beds in the main block. The 4 new operating suites, which are at present being designed, will be retained and there will be some beds for the following: thoracic surgery, neurosurgery, plastic surgery, the burns unit, outpatient investigations, and dentistry and orthodontics. The main inpatient service will eventually be moved to the site at New Cross, where it is proposed to adapt six wards to provide an acute admission and rehabilitation geriatric unit, and to build a new maternity unit. It is also planned to build on this site a mental hospital with 350 beds and a new general hospital. Once these new buildings are erected some of the smaller hospitals and units of the group, some of which are uneconomic, can be closed.

LIPIDS AND ARTERIAL DISEASE

FEW medical men find time to study Professor Hilditch's large book on *The Chemical Constitution of Natural Fats*, which is a standard reference work for chemists; but now, with Dr. Jasperson, he has produced a small monograph [2] which can be strongly recommended for those with only an evening to spare. It contains a clear account of the distribution of fatty acids in Nature, and also of *cis-trans* isomerism—aspects of organic chemistry that most medical students in the past have skipped with impunity. Nowadays, without some accurate knowledge of these subjects, it is impossible for a doctor to discuss critically with a patient the latest piece of dietary advice for those with ischæmic heart-disease. This summary by Professor Hilditch and Dr. Jasperson is a first-class piece of teaching, suitable for both undergraduates and postgraduates.

1. *World Hlth Org. tech. Rep. Ser.* 1959, no. 166. Pp. 47. 1*s.* 9*d.* Available from H.M. Stationery Office, P.O. Box 569, London, S.E.1.
2. Lipids in Relation to Arterial Disease: a summary of current biochemical evidence. By T. P. Hilditch, D.SC., F.R.I.C., F.R.S., and H. Jasperson, PH.D., F.R.I.C. Pp. 39. Obtainable from J. Bibby & Sons Ltd., King Edward Street, Liverpool, 3.

SCIENTIFIC RESEARCH IN SCHOOLS

THREE years ago the Royal Society set up a committee on scientific research in schools, with Sir Lindor Brown as chairman. Its second report shows that last year 48 schools were doing research under its auspices, receiving over £2000 in grants. All projects are carried out with the specialist advice and assistance of fellows of the society and of others who act as advisers. The committee "has been much stimulated by the continued and growing response to this scheme" and looks forward to receiving further requests from schools.

EQUIPMENT FOR THE DISABLED

THE National Fund for Poliomyelitis Research is sponsoring a reference book entitled *Equipment for the Disabled*, and it is hoped to publish it in August.

The book will be in loose-leaf form to allow later additions and deletions, and on each separate sheet there will be a photograph, written description, and, where necessary, working drawing of the apparatus.

The work of collection and preparation of material for publication is being carried out at the Nuffield Orthopædic Centre, Oxford, by Dr. Margaret Agerholm, with the collaboration of Miss E. Hollings and Miss W. Williams, and she will be grateful for suggestions from colleagues for the inclusion of special apparatus which they have found useful.

INCREASES IN SERVICE PAY

THE increases in pay for those in the Services, announced last week,[1] affect medical officers as follows:

Rank (Army only)	*Annual basic pay when first appointed*	
	Old	*New*
	£	£
Lieutenant	657	730
Captain	766	839
Major	1295	1387
Lieut.-Colonel	1660	1806
Colonel	2080	2244
Brigadier	2354	2573
Major-General	3029	3285
Lieut.-General	3759	4124

Retirement benefits have also been improved.

University of Cambridge

Dr. E. H. R. Ford has been appointed lecturer in anatomy and Dr. R. H. Adrian lecturer in physiology.

Royal College of Surgeons of England

AT a meeting of the council on Feb. 11, with Sir James Paterson Ross, the president, in the chair, Prof. John Bruce was admitted and Prof. Carl Semb (Oslo) elected to the honorary fellowship, and the honorary medal of the college was awarded to Sir Cecil Wakeley, past president.

Mr. J. D. T. Jones, Mr. R. G. Macbeth, and Mr. A. G. Cross were admitted to the court of examiners. Dr. Cuthbert Dukes was appointed Thomas Vicary lecturer for 1960, and a Hunterian professorship was awarded to Mr. P. M. Weston (West Indies). Dr. Bertram Cohen was appointed the first Nuffield research professor of dental science and Dr. G. V. R. Born Vandervell professor of pharmacology.

The following were elected to the fellowship *ad eundem*:

Isabella Forshall, P. G. Cutlack Martin, G. E. Moloney, A. W. Kay.

Diplomas of fellowship in the Faculty of Anæsthetists were granted to the following:

K. W. Dodd, G. B. Burchell, I. M. Brown, T. K. Hardy, N. H. Eve, M. R. Milne, William Braude, W. S. Dykes, J. N. Thorpe, I. W. Davidson, Sohrab Rustomji Umrigar, R. D. Davie, Nasir Husain Jafry, P. W. McCormick Mary F. West, Catherine K. Adam, Gordon Clarke, D. T. McClements, Marie M. Simpson, W. J. Colbeck, Winifred E. Elesh, C. J. R. Elliott, J. P. N. Hicks, A. B. Lodge, W. N. C. McCleery, Norman McLeod, D. D. Moir, E. D. T. Ross, P. A. Tsoi-A-Sue, D. M. Davies, G. C. Fisk, Dorothy E. Harris, D. D. Hart, P. J. W. Knell, I. M. J. Mair, R. R. Manning, Isobel Speirs, Lakshman Tisse Wijeyaratne, F. B. N. Clarke, A. T. R. Fuller, C. F. Hider, B. A. Lyder, Maung U Win, J. H. Stevens, T. H. Taylor, R. J. Thomson.

Licences to practise and the diplomas mentioned in our issue of Feb. 6 (p. 344) were conferred jointly with the Royal College of Physicians. In addition a licence to practise was conferred on Patricia S. Stephenson and the D.M.R.T. was conferred on D. S. Andrew and K. D. Neddy.

1. Service Pay and Pensions. Cmnd. 945. H.M. Stationery Office. Pp. 40. 2*s.*

University of Aberdeen

The following appointments have been made:

Dr. A. H. C. Sinclair-Gieben, senior lecturer in mental health; Dr. N. G. Fraser, lecturer in mental health; Dr. D. C. Burke, lecturer in biological chemistry; Dr. John Findlay, lecturer in anatomy.

Royal College of Physicians of London

Dr. J. D. N. Nabarro will give the Oliver-Sharpey lectures on Tuesday and Thursday, March 8 and 10, at 5 P.M., at the college, Pall Mall East, S.W.1. He will speak on the pituitary and adrenal cortex in general medicine.

University of Birmingham Medical School

Prof. J. Z. Young will give the William Withering lectures on Monday, Tuesday, and Wednesday, May 2, 3, and 4. He will speak on mechanisms of learning and form discrimination. On Wednesday and Thursday, May 18 and 19, Sir Dugald Baird will give the Ingleby lectures. He will speak on the evolution of modern obstetrics. All the lectures will be given at 5 P.M. at the Medical School, Birmingham, 15.

Horder Memorial Trust

The trustees of this memorial to Lord Horder have decided to offer a travelling fellowship every third year, of the value of £600, to enable a senior member of the medical profession to visit Commonwealth countries. It is also hoped that he will give a lecture at St. Bartholomew's Hospital or the Royal College of Physicians. The first appointment is likely to be in 1961. It is not proposed to advertise the fellowship but the trustees will appoint a selection committee early in October. The secretary of the Trust is Dr. E. M. Darmady, Central Laboratory, Milton Road, Portsmouth.

Rockefeller Foundation

During the fourth quarter of 1959 the Foundation made grants of over $12 million. Those for medical and natural sciences amounted to nearly $6 million. These included a three-year appropriation of £24,000 (about $69,000) to the London School of Hygiene and Tropical Medicine for investigations into protein malnutrition.

At the school's human nutrition laboratory and at the human nutrition research unit of the Medical Research Council the protein content of tropical foodstuffs is being studied. By experimentally producing in animals two of the severe types of protein malnutrition which occur in man, it has proved possible to bio-assay vegetable proteins for the prevention and cure of protein deficiency. A technique for expressing in quantitative terms the protein values of foods consumed by man has been developed and is being used to establish requirements of the aminoacids essential to growth and health. The supplementation of deficient diets with vegetable protein sources, such as legumes, leaf proteins, and flour residues, is also being investigated.

The Doctors' Window in Guildford Cathedral

At a meeting of the Guildford division of the British Medical Association last week, Dr. G. I. Watson, chairman of the Doctors' Cathedral Window Fund, handed a cheque for £1000 to the secretary of the Guildford New Cathedral Council.

The Society of Apothecaries contributed 55 cheques totalling £268 and the B.M.A. £105 centrally with a further £40 from the Surrey divisions. £143 was contributed by medical staffs of London teaching hospitals, while gifts from other corporate bodies totalled £104. Donations from 352 individual doctors at home and overseas amounted to £642.

Miss Moira Forsyth, the artist who made the window, was thanked on behalf of the medical profession by Dr. S. Keys, chairman of the division. The stained glass panels are now on display at the cathedral.

Laboratory Animals Centre

This centre will hold a congress at the University of Nottingham on Monday and Tuesday, April 11 and 12. A symposium on the provision of animals for cancer research will be held at 1, Wimpole Street, London, W.1, on Monday, May 23. Further particulars may be had from the secretary of the centre, M.R.C. Laboratories, Woodmansterne Road, Carshalton, Surrey.

Medical War Relief Fund

During 1958–59 six educational grants amounting to £984, and seven maintenance grants amounting to £710, were made. During the past year repayments of £1000 have been made.

Biometric Society

This society will hold a symposium in Leyden from May 10 to 13 on quantitative methods in pharmacology. Further information may be had from Mr. H. de Jonge, department of statistics, Nederlandsch Institut voor Praeventieve Geneeskunde, Wassenaarseweg 56, Leyden, The Netherlands.

Community Care of the Mentally Handicapped Child

The Metropolitan region of the National Society for Mentally Handicapped Children will hold a conference on this subject at Church House, Westminster, S.W.1, on Saturday, March 12, at 2.45 P.M. Further particulars may be had from the hon. secretary, Mr. E. R. Skoyles, 194, Kenmore Avenue, Kenton, Middlesex.

Mental Patients and the Disabled Register

Regulations made last year have removed the automatic bar to the admission to this register of all patients in mental hospitals or institutions. These patients are now eligible for admission, provided they are able to work, even though they still remain in hospital. This change was recommended by the Piercy Committee.

Hunterian Society

The annual dinner, commemorating the 232nd anniversary of John Hunter's birth, was held in London on Feb. 11.

The toast of the Society was proposed by Sir Cyril Hinshelwood, president of the Royal Society, who said he was proud that Hunter had been a fellow of the Royal Society; for, although he would have been unorthodox in any age, the key to his greatness lay in his ability to see problems in their largest possible context and in terms of basic principles. In his reply, Mr. Alec Badenoch, the president, welcomed the guests, thanked the officers of his society, and reviewed the year's activities which had been popular rather than scientific; for, like Hunter, the society was unconventional.

Dr. Kenneth Robson, proposing The Lord Mayor and Corporation, spoke proudly of the society's link with the City and its privilege of using the Mansion House for the annual oration. The Lord Mayor, Sir Edmund Stockdale, responded.

Dr. Clement Chesterman proposed The Guests and Kindred Societies. In thanking the society on behalf of the "non-Hunterians" Lord Radcliffe said he was delighted to feel that he had been invited "as a person and not as a report". He went on to recall that Hunter had been one of the first expert medical witnesses to appear in a murder trial, when he had been criticised by the judge for being unable to answer "yes" or "no"; but, Lord Radcliffe added, this was a very bad judge.

Dr. D. A. Pond will give a lecture for general practitioners at University College Hospital, London, S.W.1, on Sunday, March 6, at 10.15 A.M. He will speak on new stimulants and tranquillisers in psychiatry.

Births, Marriages, and Deaths

DEATH

TAYLOR.—On Feb. 15, Dr. James Maberley Taylor of 17, Kent Terrace, London, N.W.1.

Appointments

BLACKSTONE, I. W., M.B. W'srand: house-surgeon, The Hospital for Sick Children, Great Ormond Street, London.

CROSLAND, MARGARET M., M.B. Manc., M.C.S.P.: assistant M.O., North-East Cheshire.

FULLER, ANGELA D., M.B. Cantab., D.C.H.: assistant M.O., Middlesex (area 8).

GODDARD, PEARL, M.B. Durh., D.P.M.: assistant psychiatrist (S.H.M.O.), St James' Hospital, Portsmouth.

HOWIE, G. F. A., M.B. Edin., M.R.C.P.E., D.M.R.D.: consultant radiologist, Dundee teaching hospitals.

MACGREGOR, D. MCC., M.B. Glasg., D.P.M.: consultant psychiatrist and deputy physician-superintendent, Stratheden Hospital, near Cupar, Fife.

STANFIELD, J. P., M.D. Lpool, M.R.C.P., D.C.H.: senior medical registrar, The Hospital for Sick Children, Great Ormond Street, London.

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